

Part of a series on the clinical, bacteriological and pharmacological aspects of Bactrim therapy.

This is BactrimTM performance against E. coli, Proteus spp. and Klebsiella

These are results from clinical studies in which patients with chronic urinary tract infections (primarily pyelonephritis), more than half with obstructive uropathy, were treated with Bactrim for 10 days and evaluated at intervals of 10 to 32 days after termination of therapy. Patients were considered to have a significant bacteriological response when the urine culture revealed 10,000 or fewer colonies/ml of any single organism cultured from a midstream clean-catch specimen.

	Excellent initial response* after 10 days of therapy	Impressive response maintained 32 days after termination of therapy
in E. coli infections	97.1% of 105 patients	73.1% of 93 patients
in Proteus spp. infections	81.1% of 37 patients	60.0% of 35 patients
in Klebsiella infections	85.7% of 21 patients	65.0% of 20 patients

*Data on file, Medical Department, Hoffmann-La Roche Inc., Nutley, New Jersey

In cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible urinary tract pathogens, usually E. coli, Klebsiella, Enterobacter and Proteus mirabilis.

Bactrim

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible pathogens, usually E. coli, Klebsiella, Enterobacter, Proteus mirabilis, and less frequently, Shigella, Pseudomonas, and other species.

Note: The increasing frequency of resistant organisms limits the usefulness of antimicrobial therapy in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to sulfonamide or sulfonamide derivatives; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions have been associated with sulfonamides. Eosinophilia and agranulocytosis, much more limited but occasionally fatal, have been reported in patients with thrombocytopenia in patients with thrombocytopenia.

Side Effects: Anemia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, aplastic anemia, hemolytic anemia, and other blood dyscrasias have been reported.

Precautions: Patients should be advised to avoid alcohol and to avoid driving or operating machinery until they are free of drowsiness.

Interactions: Sulfonamides may potentiate the effects of other drugs, including oral anticoagulants, hypoglycemics, and oral contraceptives.

Adverse Reactions: Allergic reactions to sulfonamides and trimethoprim are included, even if not treated with Bactrim.

Other Adverse Reactions: Anemia, leukopenia, neutropenia, thrombocytopenia, agranulocytosis, aplastic anemia, hemolytic anemia, and other blood dyscrasias have been reported.

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A B C D

Med Trib 14

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world news of medicine and its practice—fast, accurate, complete

and Medical News

Wednesday, April 9, 1976

New Birth-Control Method Fully Effective So Far



From Yoon, I. B., Wheelert, Jr., C. R., and King, T. M.: A preliminary report on a new laparoscopic sterilization approach: The silicone rubber band technique. *Am. J. Obstet. Gynecol.* 120:132-136, 1974. Fallopian tube with one fallope ring in place shows how tube is pinched to form a "kneuckle" by specially designed laparoscope. Both tubes are occluded and one or two rings may be applied. The occluded portion may become fibrosed or degenerate and be removed by metabolic processes.

No Major Complications Develop In Fallope-Ring Sterilization Trials

By MICHAEL HERRING
Medical Tribune Staff

BALTIMORE—The fallope ring procedure, a means of sterilizing women by placing a silicone-rubber ring around a pinched segment of the fallopian tubes, has now been tested in 1,050 women, with no major complications and no pregnancies to date, according to a Johns Hopkins University School of Medicine team.

According to its developer, Dr. In Bae Yoon, Assistant Professor of Gynecology and Obstetrics, the ring, which is 2.2 mm. thick and has an inner diameter of one mm., can be applied on an outpatient basis using local anesthetics. Patients may return home in three to four hours, he said.

"A significant problem with laparoscopic cauterization of the fallopian tubes has been the incidence of bowel burns," Dr. Yoon stated. "The development of the silicone rubber band approach eliminates this potentially catastrophic complication since the requirement for the use of thermocoagulation for tubal occlusion has been eliminated."

Another disadvantage of cauterization, he pointed out, has been the permanence of the sterilization due to un-

controllable thermal damage to the fallopian tubes. The silicone rubber band, he said, keeps tubal damage to a minimum. "Tubal reopening procedures should be possible," he added.

Placement of the fallope ring is done with a special laparoscope designed by Dr. Yoon. The instrument consists of a pair of forceps inside a cylinder. Dr. Yoon explained. The fallope ring is stretched over this cylinder prior to the

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Drastic Overhaul Proposed In NY State Malpractice Law

By EDWARD GROSSMAN
Medical Tribune Staff

NEW YORK—With a warning that medicine in New York faces the possibility of "chaos" this summer, officials of the state medical society have unveiled a package of legislative proposals that would result in a drastic overhaul of malpractice law and the formation of a mutual insurance company by and for doctors.

The emergency action was prompted by skyrocketing premiums for malpractice insurance and the announce-

Extensive Mayo Clinic Study Finds:

Breast Cancer Not Associated With Rauwolfia Derivatives

Medical Tribune Report

TAMPA, FLA.—An extensive study at the Mayo Clinic has produced data contradicting earlier reports of a relationship between breast cancer and use of rauwolfia derivatives such as reserpine for management of hypertension.

In the study, conducted by Dr. W. M. O'Fallon and his associates, 449 women with initial breast cancer diagnosed during the period 1955-73 among residents of Olmstead County, Minnesota were compared with a matched control group of 475 women with cholecystitis and cholelithiasis. The controls were frequency-matched for age, date of diagnosis, and were similar in respect to parity, body build, and socioeconomic status.

No excess of breast cancer was found among women with prior use of rauwolfia derivatives, Dr. O'Fallon told the annual conference of the American Heart Association's Council on Epidemiology here. The study was undertaken, he said, to provide "a rapid response . . . to the serious need for timely data."

Among the controls, nine women had received a rauwolfia agent alone for the treatment of their associated hypertension as did seven women in the breast cancer group.

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Rapprochement In USSR-US Cancer Patterns Observed

Medical Tribune World Service

BETHESDA, Md.—Cancer incidence patterns in the Soviet Union are gradually coming to resemble those in the United States, the U.S.S.R.'s chief oncologist believes.

Prof. Nikolai N. Blokhin, here for the negotiation and signing of an agreement establishing a joint U.S.-U.S.S.R. cancer epidemiology program, said in an exclusive interview that though his country's cancer pattern is now like that of an underdeveloped nation, it is slowly shifting toward the American model.

"This is very interesting for us because in looking at your statistics, we can get some idea of which tumors will be most important for us in the future," he told MEDICAL TRIBUNE.

He cited changes in stomach and lung cancer rates in the Soviet Union as examples of the increasing similarity between Soviet and American cancer

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making rounds at press time

STANDARD HOSPITAL CARE was found in 69 of 105 hospitals nationwide that were spot-checked by H.E.W., according to government report to be published soon. Deficiencies include fire hazards, improper drug records, inadequate nursing, poor

dietary supervision. Results of survey are "astounding", says Stanley Rosenfeld, section chief for hospitals of H.E.W.'s Bureau of Insurance. Legal responsibility for monitoring quality in hospitals receiving federal monies is vested in Joint Commission on Accreditation of Hospitals, a hospital-funded private group. Hospitals cited by H.E.W. had been approved by J.C.A.H.

VD - It is uncertain whether the leveling trend in VD incidence will continue, Wendell Bradford, C.D.C. Assoc. Dir. of State Services told MT. Reported syphilis is down slightly, and increase in gonorrhea has slowed 50%. "We're nervous about predicting great success," he said, noting that cuts are proposed in Federal VD grants in 1976.

ALL SHOOK UP - Studies of medical records of 1,448 interstate bus drivers showed high incidence of back problems, varicose veins, hernias, and hemorrhoids, according to Dr. Haskell Zipperman of Southwest Research Institute, San Antonio. He told MT "whole body vibration" may be chief mechanism and is planning further studies to test hypothesis.

Bar Assn. Urges States Adopt Brain-Based Definition of Death

By EDWARD GROSSMAN
Medical Tribune Staff

CHICAGO—The House of Delegates of the American Bar Association has approved a legal definition of death and recommended its enactment into law by state legislatures.

The A.B.A. definition says, "For all legal purposes, a human body with irreversible cessation of total brain function, according to usual and customary standards of medical practice, shall be considered dead."

Dr. McCarthy De Mere, a plastic surgeon and lawyer who is Director of the Institute of Legal Medicine at Memphis State University Law School and author of the A.B.A. definition, told MEDICAL TRIBUNE that he hoped it would settle some of the controversy arising from organ-transplantation and the use of sophisticated apparatus to sustain heartbeat and respiration in the absence of brain function.

1906 Definition Has Persisted

Until now, lawyers have had to depend on the 1906 edition of Black's Law Dictionary, which defined death as the cessation of heartbeat. Legal death is still defined in 46 states according to traditional criteria of heartbeat and respiration; four states (Virginia, Kansas, California, and Maryland) have recognized "brain death" as an additional criterion, while 14 state legislatures are contemplating changes.

"Technological advances make a new definition urgently necessary," Dr. De Mere said. "The legal profession and the general public—especially relatives of the dying and dead—will be better off once it is on the books. So will the medical profession, I believe."

However, the A.M.A.'s House of Delegates is on record strongly opposing any statutory definition of death, on the grounds that physicians should be solely responsible for establishing criteria and making individual clinical determinations, and because criteria and methods may continue to change so fast that any new law may soon become obsolete.

"How can you tell what 'usual and customary' means in the A.B.A. definition?" Norman Jeddeloh, A.M.A. staff attorney, asked in an interview with MEDICAL TRIBUNE. "Standards of medical practice are different from hospital to hospital, physician to physician. I think this definition, like any statutory definition, opens up more questions than it answers. And as you know, it's easier to write a law than repeal it."

Joint Meeting to Study Issue

Mr. Jeddeloh said that the problem of defining death will be discussed at the next joint meeting of the National Conference of Representatives of the A.M.A.-A.B.A., and he expects the A.B.A. will be requested to consider withdrawing its proposal. Unless the A.B.A. agrees to do so, its definition will go to the Uniform Law Commission as the basis in drafting of a standard definition nation-wide. The Commission's members are appointed by each Governor, and charged with recommending laws to state legislatures.

Dr. De Mere contends that the definition in no way restricts physicians or impinges on their rights and duties.

"We were very careful to write a strictly legal definition, leaving to the doctor the job of making the medical determination," he said, referring to the A.B.A.'s special committee of lawyers, neurologists, neurosurgeons, and theologians.

"We also made sure to stipulate that cessation of brain function must be total—that is, not only 'cerebral death', as shown by flat E.E.G.s, but death of the brain stem as well, as evidenced by a series of neurological tests described in the Harvard criteria."

The "Harvard criteria" were drawn up in 1969 by several of the faculty of the Harvard Medical School in an attempt to modernize the determination of death. Among the criteria listed were absence of spontaneous breathing, falling arterial pressure in absence of drugs or other support, lack of reflex or response to a wide range of stimuli, and isoelectric electroencephalograms obtained over a twenty-four hour period from normochemic, non-hypothermic patients.

The official A.M.A. position, most recently stated last June, is that physicians, in using their best judgment to determine death, should be mindful of the Harvard criteria.

The A.M.A.'s displeasure with the A.B.A. move notwithstanding, some physicians have welcomed the idea of a legal definition of death.

"Legislation is not the full answer," Dr. Shelly Chou, Professor of Neurosurgery at the University of Minnesota Medical School told MEDICAL TRIBUNE, "but it is a step forward. It will make physicians more comfortable in determining death, especially in cases of transplant donors, and coun-

New Drug Lethal to Warfarin-Resistant Rats



Rats resistant to warfarin, long the standard item against rodent infestation when mixed in bait stations with food, above, are appearing. A team of British investigators has found that a new drug called difenacoum, which blocks the uptake of vitamin K, achieved complete control where all other poisons failed.

selling the patient's relatives. And in general, I'd say there was a rough consensus gradually developing among doctors anyway that irreversible brain damage is equivalent to death."

Dr. Samuel L. Kountz, Professor and Chairman of the Department of Surgery at Downstate Medical Center in New York, called the A.B.A. proposal "fantastically good." Dr. Kountz has performed kidney transplants and is active, with state senator Donald M. Halperin, in trying to amend New York law to recognize brain death.

"One problem is to educate the public and the medical profession, and I think laws like this are the best way," Dr. Kountz said. "A bigger, more ur-

gent problem is to clear up the terrible confusion and inhibitions about transplants. Many surgeons are afraid that they might be hailed into court over a technicality. The time for test cases and new laws is long overdue."

In a recent case at the Jacobi Hospital in New York City, doctors removed the kidneys from a young homicide victim who showed no brain activity but whose heart had been kept beating mechanically. The removal of the kidneys, for purposes of transplantation, was performed with the consent of the patient's parents, but it was in defiance of state law, which defines death as the termination of heartbeat and respiration, and requires autopsy in homicide.

West German Army May Enlist Woman MDs

By JAMES MAGRE
Medical Tribune World Service

BONN—If a Government proposal is accepted by the West German parliament, the first women doctors in uniform will be helping staff German army barracks and hospitals this fall.

To make this possible, the German constitution will have to be altered, because at present there are no women in uniform in the German army.

The proposal is prompted by the increasing shortage of medical staff for military duties, a Government spokesman told MEDICAL TRIBUNE here. At present the army gets around the problem to some extent through civil contracts with physicians, and through a military service obligation for all graduating medical students.

"But hiring civilian doctors on contract is proving costly, and even with the help of new medical graduates we still face a shortfall of about 600 physicians," the spokesman said.

Since the rapid turnover among medical graduates doing their military service is also a handicap, the Government aims to attract female staff on

a long-service basis. The lowest grade will be captain, with a minimum salary of about \$1,000 a month.

For Dr. Hedda Heuser, former member of the German parliament and president of the German women doctors' association, the proposal represents a major step forward in winning equality for women in the professions in Germany.

33 Serve Army as Civilians

She noted that at present there are only some 33 women physicians who work for the army as civilians, but they have only limited authority. "They could not order for example that a man be taken out of training for medical reasons," Dr. Heuser commented. As officers, she noted, they would have full authority, as well as be eligible for advancement to all ranks.

"We have been working both in parliament and in the medical profession to help win recognition of the needs of professional women," Dr. Heuser went on. "At present there are about 25,000 women physicians among Germany's 120,000 M.D.s, but a very

high percentage either drop out or never go into medical practice because of family demands."

One consequence of this, she noted, is that the few women who occupy top posts in medicine are usually unmarried.

'Too Much Improvisation'

Some progress has already been made, Dr. Heuser said. In 1972 it was finally agreed that women hospital physicians could do postgraduate work half-time, so that they could also continue to look after their families.

"But there is still too much improvisation," Dr. Heuser concluded. "The army proposal points the way to proper conditions for women doctors and I therefore welcome it."

Israeli Services Frozen

Medical Tribune World Service

JERUSALEM—Health services in Israel will be virtually frozen in 1975 at the 1974 level due to the economic situation, Finance Minister Yehoshua Rabinowitz announced in the Knesset.

\$1.013 Billion Program Launched

Health Services Planning Off to a Quiet Start

By ALAN FITZGIBBON
Special Tribune Correspondent

WASHINGTON—With little fanfare, the Federal Government has begun a new, \$1.013 billion health services planning program, which it hopes will save millions of dollars by avoiding the construction of unneeded facilities.

"I estimate that the country has 70,000 excess hospital beds," said Health, Education, and Welfare Secretary Caspar W. Weinberger. "Our long-range goal is to close those that can be closed, especially many empty obstetric and pediatric wards. But the best thing we can do is prevent unneeded facilities from being built in the first place."

The new program replaces four existing ones, three of which became well known before they legally expired last June 30.

Hill-Burton, RMP Included

The three were the 28-year-old Hill-Burton Hospital Construction Program, which will now be redirected toward aiding the construction of outpatient facilities or the modernization of hospitals in medically underserved areas; the Regional Medical Program, begun in 1965 to extend the advanced care given to heart, stroke, and cancer patients in major research hospitals to all parts of the country; and the Comprehensive Health Planning Program, which had been faulted for lacking the direction, political power, and resources that the sponsors hope the new program will have.

The fourth, a comparatively minor effort, was the experimental health service delivery systems project.

The Ford Administration strongly supported the goals of the new program as the legislation underlying it moved through Congress late last year. The Administration was worried by the country's costly surfeit of hospital beds and other health facilities, and considered better planning necessary to hold down health care costs before enactment of any national health insurance legislation, which is expected to create new demand for health care and thus increase inflationary pressures on medical costs.

New Law Effective Jan. 4

Congress passed the National Health Planning and Resources Development Act of 1974 (PL 93-641) overwhelmingly, the Senate by 65 to 18 on November 25 and the House by 236 to 79 on December 13. President Ford signed the new law on January 4, and it became effective immediately.

Largely by default, the new statute was the most important piece of health legislation enacted last year. Other major health bills died in committee or conference or were pocket-vetoed.

Despite the warm endorsement given to the legislation by both Congress and the Administration, it has not wanted for critics.

The American Medical Association, calling the program a "dangerous" and "unwarranted" intrusion on medical practice and states' rights, has threatened to fight it in court. More recently, the National Governors' Conference

Health systems agency planning

grants
State agency grants
Demonstration grants for state
rate regulation
Centers assisting planning agencies
Construction and modernization
grants
Area health services
development grants

Fiscal 1975 Fiscal 1976 Fiscal 1977

\$ 60	\$ 90	\$125
25	30	35
4	5	6
5	8	10
125	130	135
25	75	120
\$244	\$338	\$431

Expenditures (in millions of dollars) authorized in the \$1.013 billion health services planning program during its three-year statutory life.

charged that the statute's provisions showed "a clear lack of public accountability."

Several Department of Health, Education, and Welfare officials who are familiar with the legislation do not like it either. One called it a "mishmash," and another asserted that "its overlapping of jurisdictions will only compound the confusion" that the earlier comprehensive health planning program had produced.

The first step to be accomplished in setting up the new program is the designation by the nation's governors of about 200 "health service areas," which with few exceptions will have populations of between 500,000 and 3,000,000 persons, will be integrated enough "for the effective planning and development of health services," and will have at least one center each providing "highly specialized" health care.

The governors have until May 3 to draw boundary lines, and HEW will be empowered to revise them if it wishes.

'Health Service Agencies'

After the health service areas have been defined and before the middle of next year, HEW is required to designate in private, nonprofit organization, unit of local government, or public regional planning body as the "health systems agency" for each area. Each agency is to have at least five staff members, and current budget planning calls for one staff professional per 100,000 population.

The local agencies will have the task of developing long-term health objectives for their areas, preparing and carrying out annual implementation plans, reviewing and approving or disapproving applications for Federal funds for health programs within the areas, and aiding statewide health planning agencies also established by the new law.

State agency activities will include developing statewide health plans, reviewing all capital expenditures for health facilities within the state, determining the need for any new institutional health services, and reviewing the need for existing health facilities. Beginning in fiscal 1980, the law prohibits Federal payments for health resources development to states that have not satisfactorily established a state agency.

Both the local and state agencies are to be governed by councils. Three-fifths of the local council members are to be health care consumers and the

remainder are to be providers, one-third of whom must be direct providers rather than insurers. At least half of each state council's members are to be health care consumers. A National Council on Health Planning and Development is also to be established.

Construction and modernization grants—the biggest single category in the program's budget—are to be allocated to the states on the basis of their population and need for medical facilities and money, but the states will be able to use their grants only for the conversion of existing facilities to outpatient care, the modernization or construction of current outpatient facilities, or the construction of new inpatient facilities in areas of recent population growth.

20% Limit on Inpatient Facilities

States will be required to use at least 25 per cent of their allotments for outpatient facilities in medically underserved areas and will be barred from using more than 20 per cent of their allotments for construction of new inpatient facilities.

Though the agencies will be able to veto the payment of Federal funds to planned new facilities if they feel they are unneeded, they will be powerless to do anything about existing facilities that are underused except deny them funds for further construction.

What constitutes a "facility"? That is a touchy question because so many different interests are involved. According to Eugene J. Rubel, HEW's health planning chief, hospitals definitely come within the program's scope and clinical laboratories do not.

"Large group practices may be included," he said, referring to funds for the buildings that house them, "but solo practices will not. We haven't yet decided on blood banks."

Mr. Rubel, whose official title is acting associate director for health resources planning in the Bureau of Health Resources Development of HEW's Health Resources Administration, is, at 34 years of age, the foremost *Wunderkind* of the Federal health apparatus.

It is widely said that within a few months he will be appointed the director of a new health planning bureau to be spun off from and become co-equal with the Bureau of Health Resources Development, whose other main interest is the Federal health manpower program.

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CLINICAL NEWS NOTE: "A significant problem with laparoscopic cauterization of the fallopian tubes has been the incidence of bowel burns. The development of the silicone rubber band approach eliminates this potentially catastrophic complication since the requirement for the use of thermocoagulation for tubal occlusion has been eliminated." (Dr. In Bae Yoon, see page 1.)

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Acupuncture Pain Relief Indicated to Be Independent of Site of Needle Insertion

Medical Tribune World Service

WINNIPEG, MAN.—Preliminary results of a study of 91 acupuncture patients with chronic pain indicate that relief is not dependent on the site of needle insertion and that there is no more relief when the patients can look at the therapists than when they cannot.

Dr. Charles Godfrey, director of rehabilitation medicine, Wellesley Hospital, Toronto, reported these results to the annual meeting of the Royal College of Physicians and Surgeons of Canada.

A total of 82 per cent of the patients experienced noticeable relief, 69 per cent considerable relief, 61 per cent con-

siderable and lasting relief, and 30 per cent had their pain reduced "very significantly" to only 10 per cent of what it had been before, Dr. Godfrey said.

Pain Caused by Osteoarthritis

The patients, between 25 and 50 years old, had had chronic pain for more than three months and less than two years, the study showed. The pain was caused by osteoarthritis of elbows, shoulders, knees, or low back, Dr. Godfrey reported.

He and his colleagues found that there was as much relief from pain when the needles were inserted in other than classical sites. In fact, the thera-

pist did not know the actual site of the patient's pain, Dr. Godfrey said.

Further studies are planned, Dr. Godfrey said.

Coauthors of the study were Drs. K. Livingston, I. MacNab, H. A. Smythe, R. MacDonald, H. Moldofsky, and I. Raudzens.



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EDITORIAL CAPSULES

... brief summaries of editorial comments in current medical or scientific journals.

Acetaldehydism?

"Prolonged, excessive use of alcohol (ethanol) is associated with alterations in structure and function of number of organs. These disorders have given rise to controversy over the relative importance of a direct toxic action of alcohol and the effects of nutritional deficiencies that are often associated with chronic alcoholism. Recent evidence suggests that disorders of the liver, heart, and bone marrow, though aggravated and accelerated by nutritional deficiencies, are probably caused by cytotoxic actions of alcohol. The biochemical basis of this cytotoxicity is uncertain. . . . Korsten and his colleagues suggest that acetaldehyde, a metabolite of ethanol and a known potent cytotoxin, may contribute to the pathogenesis of these alcoholic disorders.

Korsten et al. have demonstrated the expected plateau of blood levels of acetaldehyde in the face of varying blood ethanol levels; they have also clearly established that patients with alcoholism can manifest this plateau at a higher level than nonalcoholic persons, confirming earlier, perhaps less rigorous, studies.^{1,2} This demonstration of higher blood levels of acetaldehyde in habitual drinkers satisfies the dose-response requirement and effectively removes a constraint that has been imposed upon hypotheses of alcohol's toxicity. It has now become important to know much more about the metabolism of acetaldehyde and the characteristics of its cytotoxicity (Editorial, Neil H. Raskin, M.D., New Eng. J. Med. 292:422, Feb. 20, 1975).

Attitudes on Child Abuse

"The approach to the problem of child abuse seems to be going through the same evolutionary phases that characterized alcoholism treatment programs. Not too long ago, alcoholics who ran afoul of the law were placed in jail for a 'drying out' period. Gradually it was realized that this legal approach neither solved nor prevented the problem. . . . Today alcoholism is viewed as a disease, with psychological, social, financial, and medical implications.

"The approach to the treatment of child abuse is now in a transition period. We are getting away from the legal, punitive approach, in favor of a more comprehensive method of dealing with the problem. Ideally, with the eventual establishment of a national system of child abuse centers, the entire gamut of the battered child syndrome, including its social, psychological, and medical aspects, will receive consideration in treatment programs. In addition, further research into the psychosocial aspects of this 'disease' will help us reduce its incidence and tragic consequences through preventive measures." (Special article, Robert H. Woodworth, D.O., Oklahoma State Medical Journal 67:474, Nov., 1974)

IN CONSULTATION

What's New and Important in Management of Heart Failure?



The Consultant

DR. JAY N. COHN
Professor of Medicine,
Head, Cardiovascular Section,
University of Minnesota Hospital,
Minneapolis, Minn.

MANAGEMENT of heart failure from all causes and of all degrees of severity has traditionally involved the administration of inotropic drugs (digitalis, or for more acute situations, sympathomimetic drugs) and diuretics. Recent studies have demonstrated the effectiveness of vasodilator drugs in improving left ventricular

performance in patients with heart failure. Sodium nitroprusside administered intravenously has proved to be an effective agent for treating patients with severe heart failure complicating myocardial infarction, ischemic heart disease, cardiomyopathy or mitral insufficiency. This drug reduces the resistance (impedance) against which the left ventricle must eject by dilating peripheral arteries. Its effect on the failing heart is to increase stroke volume and cardiac output at the expense of a small reduction in arterial pressure. Such therapy also reduces the work of the left ventricle and its oxygen consumption. Whether sodium nitroprusside will be effective treatment for myocardial infarction by reducing myocardial ischemia and thus limiting infarct size is under study.

The application of long term vasodilator therapy for the treatment of chronic congestive heart failure is limited by the availability of potent, orally effective vasodilator drugs. Various nitrates are now being utilized for this purpose, but results of carefully controlled studies must be evaluated before their place can be established.

Please discuss the use of nitroglycerin in acute myocardial infarction.

Nitroglycerin has long been considered to be contraindicated in patients with acute myocardial infarction because of the risk of hypotension. It is now recognized that a nitroglycerin effect could be beneficial by reducing the work of the heart, improving its performance, and relieving ischemia in the peri-infarction zone. However, severe hypotension also could aggravate ischemia by reducing coronary blood flow. Administration of controlled amounts of nitroglycerin in order to produce only a slight fall in arterial pressure seems to be safe and may be beneficial. The problem with sublingual nitroglycerin is that the response to a standard dose may vary from patient to patient. Administration of the drug in ointment form to the skin may allow a little better control of dosage. Keeping the patient supine should reduce the risk of severe hypotension, but if nitroglycerin is to be employed in these patients it should be started in very low doses and titrated upward until the desired effect is attained without an inordinate fall in blood pressure. The most precise way to determine the "effective" dose is to monitor the pulmonary arterial pressure and to titrate to a 25 to 50 per-

cent fall in an elevated pulmonary wedge pressure.

What is the place of norepinephrine, isoproterenol and other beta-adrenergic drugs in cardiogenic shock?

Beta-adrenergic stimulatory drugs increase myocardial oxygen consumption, and this effect may be deleterious in the acutely infarcted ventricle. On the other hand, if intra-arterial pressure is low the drugs may correct hypotension and thereby increase coronary blood flow and myocardial oxygen delivery. In addition, if the drugs increase cardiac output, the deleterious effects of impaired regional perfusion may be corrected. Thus, these drugs are "double-edged swords" and their effects must be carefully monitored in each patient to determine if a beneficial or deleterious response is occurring. In

general the best response would be expected to the drug which supports arterial pressure at minimally effective levels (usually 90-100 mm. Hg systolic pressure), with the least degree of vasoconstriction and with the least increase in heart rate. The physician may choose between norepinephrine, metaraminol, epinephrine, glucagon, dopamine, or isoproterenol. Two new experimental drugs, esproquin and dobutamine, have the advantage of considerable inotropic effect without much increase in heart rate. Monitoring the response to these drugs should include measurement of hourly urine output, skin temperature, sensorium and blood gases. Experience suggests that if a one to two-hour infusion of these drugs does not produce a sustained improvement of the circulation in the patient with myocardial in-

Continued on page 6

Medical Tribune

Sexual medicine today

where have we been?
where are we going?

don't miss next week's sexual medicine today

Santo Domingo gender puzzle: "At puberty . . . their voices gradually deepen, their muscles expand . . . their 'clitoral-like' phallus becomes a functional penis and they express normal sexual interest in females."

Exclusive interview with Dr. Mary Calderone: The dynamic founder of the Sex Information and Education Council of the United States talks about the "great role" of physicians in establishing the "right to be sexual"; the problems of pornography; permissiveness; and the need to distinguish between sex education, sex counseling and sex therapy. Part II

Establishing sex-therapy standards: What happens when sex therapists meet to discuss their problems—scientific, professional, ethical.



from tension headache *

Let Fiorinal help release the patient from the aching, pressing, painfully tight feeling of tension headache. Its analgesic components help relieve pain while its sedative component helps relax the patient.

ANALGESIC PLUS SEDATIVE
Fiorinal

Each tablet or capsule contains:
Sandoval® (butalbital) (Warning: May be habit forming) 50 mg.;
caffeine, U.S.P., 40 mg.; aspirin,
U.S.P., 200 mg.; phenacetin,
U.S.P., 130 mg.

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: For use to relieve pain, in "conditions in which combined sedative and analgesic action is desired, such as: nervous tension and sleeplessness associated with pain or headache." Final classification of the less-than-effective indications requires further investigation.

Contraindications: Hypersensitivity to any of the components.

Precautions: Due to presence of a barbiturate, may be habit forming. Excessive or prolonged use should be avoided.

Side Effects: In rare instances, drowsiness, nausea, constipation, dizziness, and skin rash may occur.

Adult Dosage: One to two tablets or capsules, repeated if necessary up to 6 per day, or as directed by physician.

Before prescribing, see package insert for full product information.

RAMBO PHARMACEUTICALS, EAST MANOVER, N.J. 08046



IN CONSULTATION

Continued from page 3
faret shock, mechanical cardiac assistance should be considered.

What is the current status of intra-aortic balloon counterpulsation in cardiogenic shock in acute myocardial infarction?

Intra-aortic balloon counterpulsation is the most effective, reliable and practical means of improving cardiac function and myocardial metabolism when hypotensive shock has developed after acute myocardial infarction. The earlier this therapy is applied the more likely the progressive circulatory deterioration

of shock will be reversed. In most studies balloon assist has been instituted after medical therapy has apparently failed. The salvage rate in such patients has been quite low (less than 20 per cent). Some patients have been stabilized for a number of hours so that angiography and bypass surgery could be performed. Each of these interventions has resulted in some salvage of life, but even with the best medical and surgical therapy the prospect for the patient who has already developed shock is dismal. Nonetheless, when confronted with a potentially salvageable patient with cardiogenic shock the physician who has these rational, invasive modes of therapy available to him will want to apply them as quickly as possible. A more fruitful direction for research, however, would seem to be attempts to limit infarct size and pre-

Next in Consultation

DR. CLAUDE A. FRAZIER, M.D., P.A. of Asheville, N.C. Author of *Coping with Food Allergy*, published by Quadrangle Books, New York Times Publishing Co., New York; and *Insect Allergy*, published by Medical Examination Publishing Co., will answer questions on food allergy and the role of emotional stress, when food allergy should be considered as an etiologic factor, use of a basic elimination diet, the current status of skin testing and desensitization, and the possible role of food additives as allergens.

vent the development of shock in patients with acute myocardial infarction who are at highest risk. A number of approaches are being evaluated.

Closed-Circuit Bingo



To stimulate morale of patients, closed-circuit TV bingo has been introduced at Outer Drive Hospital in Lincoln Park, Mich. Volunteers select bingo letters on camera, above, while patients follow game in their rooms, below. The games are particularly valuable in relieving the depression of chronically ill patients.



Usual Throat Cultures Termed Unreliable

Medical Tribune Report

CHICAGO—Ordinary throat cultures may fail to detect pathogenic organisms causing tonsillitis, and therefore should not be relied upon uncritically to determine medication of choice, according to Northwestern University team of investigators.

In a study of 100 children with severe throat disorders on whom tonsillectomy was performed, Drs. Annette M. Lotter and George W. Allen, Instructor and Associate Professor at Northwestern University School of Medicine, found that cultures of the parenchyma of the excised tonsil sometimes revealed the presence of beta-hemolytic streptococcus, *Staphylococcus aureus*, and *Hemophilus influenzae* that had not been detected in preoperative cultures taken by wiping the tonsil surface.

"We don't conclude from this that throat cultures are useless," Dr. Lotter told MEDICAL TRIBUNE. "Cultures taken from the tonsil crypts of an anesthetized child are more reliable than those from a small portion of the tonsil surface. All cultures may be diagnostically helpful when positive, though not absolutely reliable when negative."

test in patients with suspected or known allergy. Use with caution in otitis externa; avoid using in otitis media, presence of perforated drum, known dermatologic sensitivity or other allergic manifestations. Avoid undue exposure of large skin areas to the drug.
Adverse Reactions: Reported incidence in clinical studies* is about 1%, ranging from mild erythema to severe eczematoid reaction of external ear and periauricular tissues; all reported uneventful resolution and no sequelae. *Bibliography and detailed information available upon request. **Purdue Frederick**
GOVERNMENT 1974. THE PURDUE FREDERICK COMPANY, ELKHART, INDIANA 46517

CERUMENEX DROPS

(methanolamine polypeptide oleate condensate 100% in propylene glycol with chlorbutanol 0.5%)

- Clears the ears prior to ear examination, otologic therapy or audiometry.
- Specific cerumenolytic action—excellent results reported in over 90% of 2,700 adult and pediatric patients.*
- Needs no repeated instillations for several days, unlike some other agents.

Indications: Removal of cerumen; removal of impacted cerumen prior to ear examination, otologic therapy or audiometry. **Contraindications:** Previous untoward reaction to the drops; positive patch test. **Precautions:** Patch

Fill external canal with the drops, with patient's head tilted at 45° angle;

Insert cotton plug and allow to remain for only 15 to 30 minutes;

Remove plug and gently wash ear with lukewarm water, using soft rubber syringe.

Current Opinion

"Moratorium on Reckless Statements" and More Study of ADRs Urged

MEDICAL TRIBUNE presents a "Current Opinion" from Dr. Dana L. Farnsworth, Professor Emeritus of Harvard Medical School, and Chairman of the Board of Directors of Medicine in the Public Interest which recently published an important "Report of Adverse Drug Reactions." Highlights of the Report were presented in recent issues of MEDICAL TRIBUNE. Dr. Farnsworth's comments, which describe how the study came to be published, summarize the current opinion of many leading physicians on this critical problem.

THE STUDY of adverse drug reactions, released by Medicine in the Public Interest, a non-profit organization, was prepared by Drs. Fred Karch and Louis Lasagna of the University of Rochester School of Medicine and Dentistry. Their investigation concludes that no valid data exist to support widely circulated stories that scores of thousands of Americans are unnecessarily harmed or die because of side effects of modern medications and calls for "a moratorium on reckless statements and estimates."

The study was stimulated by Senator Edward M. Kennedy's interest in obtaining objective expert evaluation of the problem of adverse drug reactions. At the hearings of his Senate Health Subcommittee some of the testimony offered resulted in frightening newspaper stories which extrapolated estimates by non-researchers of 120,000 and in one instance 140,000 deaths. The Medicine in the Public Interest report, which had the benefit of consultation with American researchers whose data were used by others who made the exaggerated extrapolations, indicates that such projections are invalid and that considerable additional data is needed to define the problem and lay the basis for educational efforts.

Character of Most ADRs

As to severity and type of side effects, "The majority of reported ADRs are minor functional gastrointestinal disturbances, and together with rash, itching, drowsiness, insomnia, weakness, headache, tremulousness, muscle twitching and fever" account for 60 to 71 per cent of reported adverse drug reactions. "Interpretation of these data is impossible... especially since one or more of these same symptoms were found... in up to 84 per cent of healthy individuals taking no medications at all." The problem is further complicated in that many of the "symptoms reported before treatment and after placebo" are similar to those reported as adverse drug reactions.

Among those who participated in the study and who serve as consultants for this report were leading scientists whose data were invalidly extrapolated and whose statements have been expanded upon or used without their qualifications as well as some who have taken issue with prior estimates of the incidence of ADRs. Among the participants in the MPI study were professors of medicine Leighton Cluff of the University of Florida and Alvan Feinstein of Yale; professors of medicine and pharmacology Daniel Azarnoff of Kansas University and Jan Koch-Weser of Harvard; chief of clinical pharmacology Kenneth Melmon of the University of California, and professor of statistics Paul Meier of the University of Chicago.

Some Conclusions

These conclusions were sharply defined in the words of the report:

• "Current estimates of the magnitude and cost of the adverse reaction problem are completely unreliable because [their] data base... is incomplete, unrepresentative, uncontrolled and not operationally identified." In the literature "one finds that the agents implicated in adverse drug reactions are not the newest drugs but such time-honored agents as digitalis, penicillin and insulin... Most reported fatal reactions appear to be associated with 'older, standard drugs'... In more than 75 per cent... the drug had been available in medical practice for more

than 30 years." Of 27 fatalities recorded in four studies, three were related to over-the-counter self-medication.

• "Many fatalities allegedly attributed to adverse drug reactions occur in gravely ill patients with ultimately fatal underlying diseases."

• "Most [adverse] reactions are difficult to categorize unequivocally as to cause."

Foreign-Educated Students Charge Blacklist



Wearing hoods to protect their identities, four white-coated medical students told a recent press conference in New York City that they have been "virtually blacklisted" by state medical facilities because they were trained in foreign medical schools. The students appeared at the request of State Assemblyman Charles E. Schumer (center), sponsor of a bill to guarantee foreign-educated state residents admission to clinical training programs at state schools.

Parotid Saliva Test Devised To Detect Pancreas Disease

Medical Tribune World Service

MEXICO CITY—A simple, rapid, "reasonably accurate" diagnostic test for pancreatic disorders by the examination of parotid saliva chemistry, developed by Japanese investigators, was presented here at the Fifth World Congress of Gastroenterology.

The procedure consists of measuring salivary output, maximum bicarbonate concentration, and amylase secretion. Following a single pilocarpine injection, consecutive five-minute samples are collected over a 25-minute period and tested.

It was established on the basis of animal and human studies, the investigators reported, that a decrease in these three parameters correlates closely with the presence of pancreatitis and other forms of pancreatic disease. Saliva test findings were corroborated histologically and by electron-microscopy.

Test Found 82.5% Accurate

The test was carried out in 34 patients with pancreatic disorders, 63 patients with nonpancreatic disease, and 16 healthy persons. Diagnoses of the 97 patients with pancreatic and nonpancreatic disease were confirmed by laparotomy.

Values outside normal ranges established for healthy subjects and those with nonpancreatic disease were defined as representing pancreatic disorders.

The saliva test was found to be accurate in diagnosing pancreatic disorders in 28 of the 34 patients in this category (82.5 per cent).

A comparison with the pancreozymin-secretin (P-S) test, regarded as the most useful method available for the diagnosis of pancreatic disease, was made in 12 of the patients with pancreatic disorders and 10 with nonpancreatic illness. In the first group the P-S test was 75 per cent accurate, as against 83.3 per cent for the saliva test. In the second group the findings were 100 per cent accuracy for the saliva test and a high percentage of false positives for the P-S test (in four patients

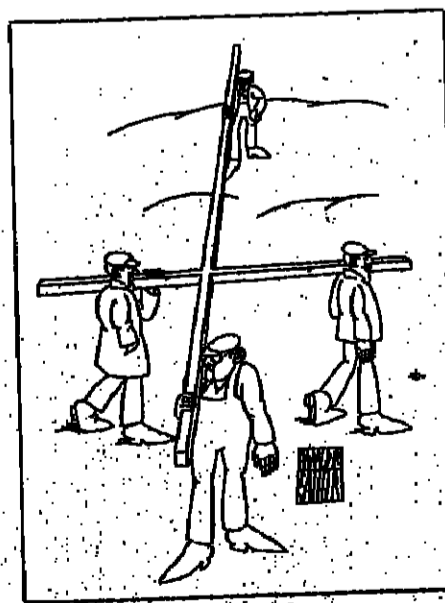
with biliary tract disease and one with duodenal cancer). Overall, the accuracy of the P-S test was 50 per cent and of the saliva test 90.9 per cent.

It was noted by Dr. Goro Kakizaki, of the Akita University School of Medicine, who developed the test, that in some cases where abnormally high salivary test values were found, the parotid glands were histologically hypertrophic and the patients had a long history of diabetes.

Histologic changes of the parotid glands were atrophic and degenerated in patients with hypofunction on salivary test and hypertrophic in those with salivary hyperfunction.

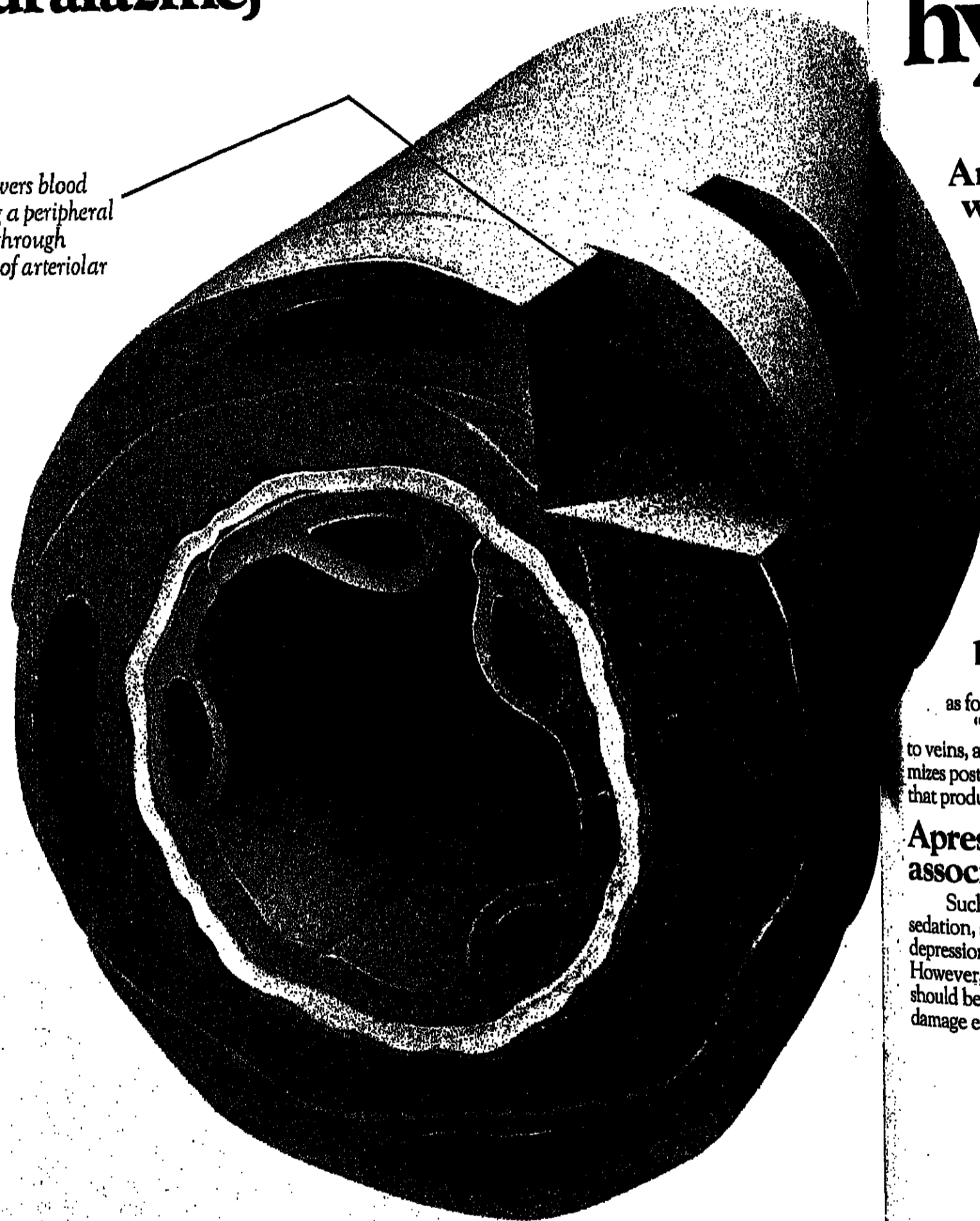
"At the moment," Dr. Kakizaki commented, "we do not know the precise mechanism by which parotid gland function is increased in these patients. Although there are several possible explanations, we are tempted to speculate that in the early stage of pancreatic disorders, parotid gland function is diminished and, conversely, comes to manifest hyperfunction as pancreatic damage progresses... We think that this hyperfunction of the parotid gland might represent a compensatory mechanism for pancreatic dysfunction."

Collaborating in the studies were Drs. Takayuki Saito and Toyokichi Maeta.



Apresoline®...where the action is in treating hypertension (hydralazine)

Apresoline lowers blood pressure by exerting a peripheral vasodilating effect through a direct relaxation of arteriolar smooth muscle.



An antihypertensive idea whose time has come

Doctors who treat hypertension are increasingly interested in the one oral drug that has a mechanism of action exclusively its own — Apresoline.

Apresoline is in an antihypertensive class by itself because it reduces blood pressure through a unique mechanism. Acting at the ultimate site of hypertension, it directly relaxes arteriolar smooth muscle to decrease peripheral vascular resistance and arterial pressure. As blood pressure falls, there is an accompanying rise in cardiac output and rate.

Apresoline also maintains or increases renal and cerebral blood flow.

Apresoline minimizes postural hypotension

Nickerson¹ describes the action of Apresoline as follows:

"A preferential effect on arterioles, as compared to veins, allows the increase in cardiac output and minimizes postural hypotension; the latter is much less than that produced by agents blocking sympathetic nerves."

Apresoline avoids side effects associated with other agents

Such untoward reactions as drowsiness, lethargy, sedation, sexual dysfunction, and exacerbation of mental depression are not usually encountered with Apresoline. However, as with any antihypertensive agent, hydralazine should be used with caution where advanced renal damage exists.

Apresoline helps tailor the regimen to the patient

When Apresoline is added to an existing antihypertensive regimen, it introduces a different and complementary pharmacologic approach to the control of your patient's hypertension.

Apresoline thus affords the physician a variety of combinations with which he can construct regimens more closely molded to individual requirements. According to Freis,² such a combination of drugs, each with a different antihypertensive mechanism, is the most effective way to control blood pressure. This may also permit lower drug dosages.

Apresoline lends itself admirably to the contemporary antihypertensive rationale and its therapeutic goals: more vigorous and more effective control of blood pressure through a plurality of mechanisms.

Apresoline: used effectively in the VA studies

Apresoline was one of the three basic drugs used in two published VA cooperative studies.^{3,4}

References: 1. Nickerson M. Antihypertensive agents and the drug therapy of hypertension. In Goodman LS, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 4. New York, The Macmillan Company, 1970, p 729. 2. Freis ED. Hypertension: a controllable disease. *Clin Pharmacol Ther* 13:627-632, 1972. 3. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202:1028-1034, 1967. 4. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressure averaging 90 through 114 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213:1143-1152, 1970.

Next page: Apresoline (hydralazine) and the Hypertension Task Force

Apresoline® hydrochloride (hydralazine hydrochloride)

TABLETS
Essential hypertension, alone or as an adjunct.
CONTRAINDICATIONS
Hypersensitivity; coronary artery disease; mitral valvular (rheumatic) heart disease.
WARNINGS
Chronic administration of doses over 400 mg per day may produce an arthralgia-like syndrome.

ing to a clinical picture simulating acute systemic lupus erythematosus. This may also occur at lower doses. Most of these reactions are reversible upon withdrawal of therapy, but long-term treatment with steroids may be necessary and residues have been detected many years later. Complete blood counts, L.E. cell preparations and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy, even though patient is asymptomatic. These studies are also indicated in the presence of any unexplained symptoms.
Use MAO inhibitors with caution.

Usage in Pregnancy
The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.
PRECAUTIONS
Use cautiously in suspected coronary artery or other cardiovascular diseases, cerebral vascular accidents, and advanced renal damage. Postural hypotension may occur, and the pressor response to epinephrine may be reduced.
Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyridoxine effect

and addition of pyridoxine to the regimen if symptoms develop.
Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy. Periodic blood counts are advised during prolonged therapy.
ADVERSE REACTIONS
Common: Headache; palpitations; nervousness; dizziness; diarrhea; tachycardia; angioedema; vomiting; diarrhea; tachycardia; angioedema; purpura; leukopenia; agranulocytosis; and lacrimation; conjunctivitis; peripheral neuritis.

evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremor; muscle cramps; psychotic reactions characterized by depression, disorientation, or anxiety; hyperreflexia (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and, rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; also, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paralytic ileus; and responses.

DOSEAGE
Initiate therapy in gradually increasing dosages, adjust according to individual response. Start with 10 mg 4 times daily for the first 2 to 4 days, increase to 25 mg 4 times daily for balance of first week. For second and subsequent weeks, increase dosage to 50 mg 4 times daily. For maintenance, adjust dosage to lowest effective level.
The incidence of toxic reactions, particularly the L.E. cell syndrome, is high in the group of patients receiving large doses of Apresoline.
In a few resistant patients, up to 300 mg Apresoline daily may be required for a significant antihypertensive effect.

In such cases, a lower dosage of Apresoline combined with a thiazide, reserpine, or both may be considered. However, when combining therapy, individual titration is essential to insure the lowest possible therapeutic dose of each drug.
HOW SUPPLIED
Tablets, 10 mg (pale yellow, dry-coated); bottles of 100 and 1000.
Tablets, 25 mg (deep blue, dry-coated); bottles of 100, 500, and 1000.
Tablets, 50 mg (lavender, dry-coated); bottles of 100, 500, and 1000.

Tablets, 100 mg (peach, dry-coated); bottles of 100.
Consult complete literature before prescribing.
CIBA Pharmaceutical Company
Division of CIBA-GEIGY Corporation
Summit, New Jersey 07901

C I B A

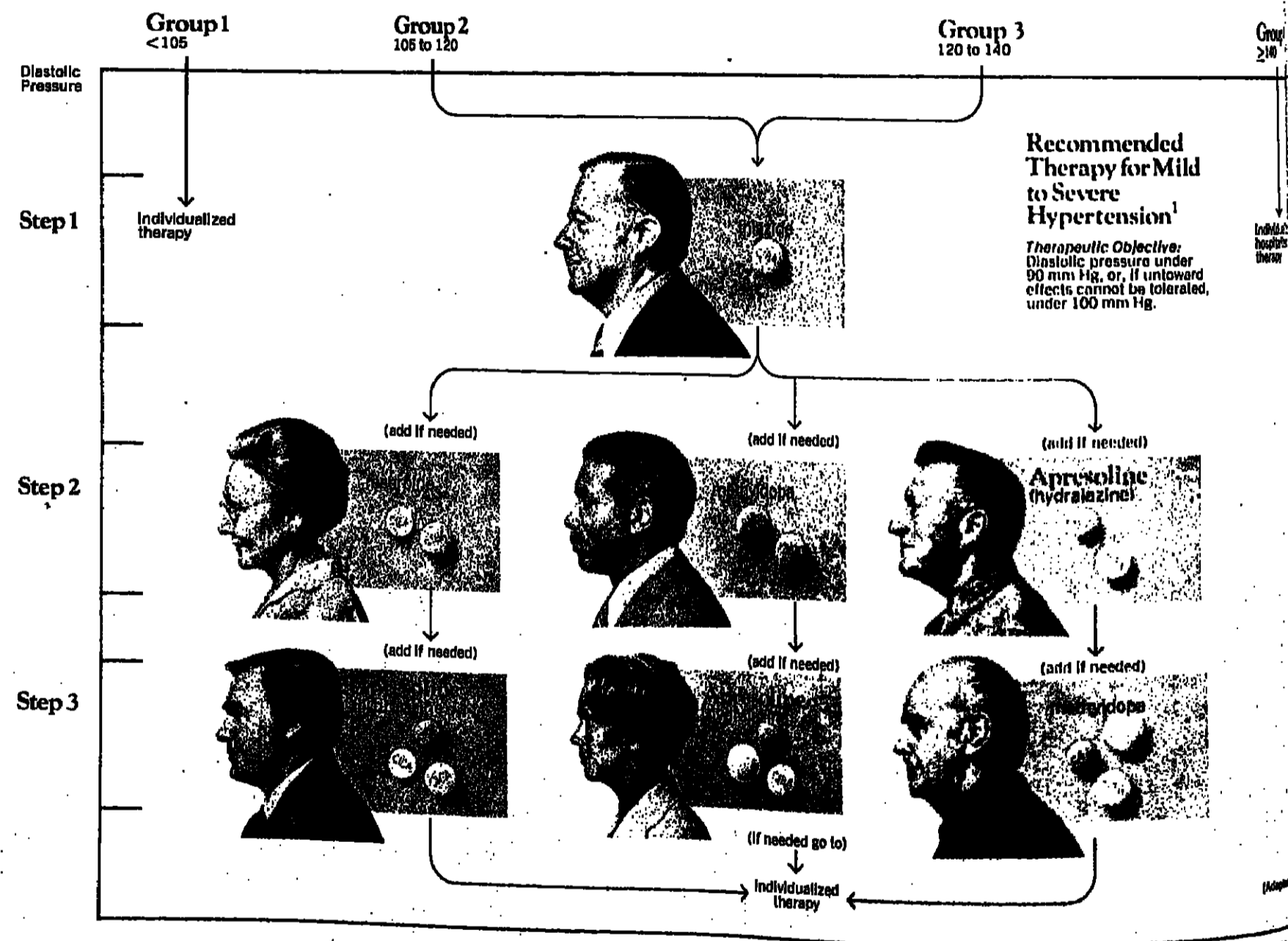
Apresoline... (hydralazine) part of the Hypertension Task Force "plan of action"

In September 1973, Task Force I of the National High Blood Pressure Education Program recommended a series of antihypertensive regimens for groups with hypertension ranging from mild to severe. Hydralazine—used in combination with sympathetic-inhibiting and/or diuretic antihypertensive

agents—was a specific recommendation for "second step" and "third step" therapy in patients with diastolic pressures ranging from 105 to 140 mm Hg. Hydralazine played a prominent role in the Task Force regimens because of its compatibility with almost any antihypertensive regimen. For

Apresoline can be combined advantageously with nearly all diuretics and sympathetic inhibitors.

Reference: 1. Report of Task Force I, National High Blood Pressure Education Program: Recommendations for a National High Blood Pressure Program Data Base for Effective Antihypertensive Therapy, Sept. 1, 1973. CHEW Publication No. (NIH) 74-559.



Apresoline (hydralazine)
...acts directly at the ultimate
site of hypertension
...brings something
special to almost any
antihypertensive
regimen

For brief prescribing information,
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Wednesday, April 9, 1975

MEDICAL TRIBUNE

11

The Only Independent Weekly Medical Newspaper in the U.S.

Medical Tribune

and Medical News
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Limitations of Associations

It is of great importance that the study at the Mayo Clinic reported on page one of this issue of MEDICAL TRIBUNE found no relationship between the incidence of breast cancer and the therapeutic use of rauwolfia derivatives. This is in contradiction to the report from the Boston Collaborative Drug-Surveillance Program, which seemed to find such an association, as did two other such retrospective studies of hospital populations.

It is of even greater importance to know whether any credence at all can be given to reports of associations, whether positive or negative, based on hospital experiences.

In all of the studies mentioned, four-fold tables of analysis were utilized to show the incidence of use of rauwolfia derivatives by patients with breast cancer as compared with a control group. At the Mayo Clinic, patients with cancer of the breast were compared with patients with cholecystitis and cholelithiasis. Of the cancer patients, 7.6 per cent had been receiving rauwolfia derivatives; 8.9 per cent of the patients with gallbladder disease were also under treatment with rauwolfia derivatives. The Boston study, on the other hand, found that 7.3 per cent of patients with breast cancer gave a history of taking a reserpine-containing drug while only 2.2 per cent of matched surgical controls and 2.2 per cent of matched medical controls did.

In 1946, Dr. Joseph Berkson, who then headed the division of biometry and medical statistics at the Mayo Clinic, published in the *Biometrics Bulletin* a paper titled, "Limitation of the Application of Fourfold Table Analysis to Hospital Data." He noted the prevalence of the notion that cholelithiasis was a provocative agent in the causation or aggravation of diabetes and that in certain circles, cholecystectomy was being performed as a treatment for diabetes. Dr. Berkson reviewed the data in his hospital for the incidence of cholecystitis among diabetic patients and compared this with the incidence of cholecystitis among patients with "several refractive errors of the sort for which patients come to the clinic for glasses." He found an incidence of cholecystitis of 4.86 per cent among the diabetic group and of 2.54 per cent among the control group with refractive errors. So that would have seemed to bear out a relationship of cholecystitis to diabetes.

But, said Dr. Berkson, let us set up a theoretical general population from which the hospital population comes. Let there be no correlation among the three diseases, cholecystitis, diabetes, and refractive errors. "We shall suppose," he added, "that associated with

each particular disease there is a definite probability that its victims will be selected for the hospital." This is the admission rate—a selection rate—for a disease and, as is well known, hospitals differ greatly in their admission rates for particular diseases.

Dr. Berkson then proceeded to show how slight differences in the selective forces for admission of patients into a hospital can create a spurious association of one disease with another as compared with the association in a control group even though there is no correlation among them.

One can do no better than quote Dr. Berkson's comments in this classic paper: "The assumption made in the text that a probability can be assigned to every disease, which gives the chance that a patient suffering from that disease alone, will come to the hospital is, I think, in general accord with the actual mechanism by which such a patient is selected for the hospital population. The assumption that these probabilities operated independently in an individual who is suffering from more than one disease is doubtless oversimple. In general, we may guess that if a patient is suffering from two diseases, each disease is itself aggravated in its symptoms and more likely to be noted by the patient. So far as this difference of fact from assumption goes, its effect would be to increase relatively the representation of multiple diagnoses in the hospital, and in general to increase the discrepancy between hospital and parent population, even more than if the probabilities were independent.

"It appears from the development that it is hazardous to apply in a hospital population the method of the fourfold table analysis for an inquiry into the correlation of diseases. This applies also to other similar problems, as for instance whether the incidence of say, heart disease, is different for laborers and farmers, if it is known that laborers and farmers are not represented in the hospital in the proportion that they occur in the community."

He goes on to say: "... there does not appear to be any ready way of correcting the spurious correlation existing in the hospital populations by any device that does not involve the acquisition of data which would themselves answer the primary question."

He emphasized that the spurious correlations "are the result merely of the ordinary compounding of independent probabilities."

Hospital populations are not random samples of the general populations. To draw conclusions about associations between diseases among them is fraught with uncontrollable errors.



"Well, that's the way it pans out with the old computer. However, I'll be only too happy to give you a second opinion."

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LETTERS TO TRIBUNE

Drinking Legislators

With the minimum reduction in the death rates due to the lowering of speed rates on our highways we may have hope in reducing the approximately 50 per cent death rate from drunken driving.

Following the publicity which was given to the law enforcement officers who were picking up our representatives in Sacramento, we can see that these gentlemen who are to protect us are really some of the worst offenders. To require restrictions upon drunken driving, we cannot rely upon drunks to legislate the laws to protect their victims. It is about time that the non-drinkers in our legislature take the problems to the voters and let us vote out the drinkers who prevent the augmentation of legal sanctions which allow this carnage.

Maybe Nader's group could issue a list of drinkers and non-drinkers in the California legislature and we could somehow do something from the "grass roots" level.

JAMES S. DEVINE, M.D.
Santa Monica, Calif.

Pleated IU Membrane

I should like to clarify a point concerning development of the pleated intrauterine membrane (MT, Feb. 5). The device, and its subsequent prototypes, were developed by Battelle Northwest Pacific Laboratories (Battelle Memorial Institute) in Richland, Wash.

The International Fertility Research Program (IFRP) is a research organization and in this capacity has acted as an independent evaluator of the pleated intrauterine membrane. We feel it important to note this difference to avoid any misunderstanding.

GEORGE H. STATHOS
Acting Director, IFRP
Chapel Hill, N.C.

Practicing Without License?

I defy Dr. Denenberg (MT, Mar. 5) to cite even one example of where a "controlled" monopoly such as he proposes has been able to provide services or goods more efficiently than competitive capitalism. Does the VA provide

care at cheaper unit costs than the Philadelphia "Blues"? Does the military?

Further: Does Dr. Denenberg seriously believe that "consumers" should control the "costs" of medical practice? Consumer input in the form of state appointed medical "experts" has already made a shambles of the medical program. Does he propose enlarging this to the Blues? Consumers have already been responsible for such giant leaps forward as the inclusion of Chiropractic in Medicare. If they "control" the Blues, we would all soon be practicing medicine under the direction of those practicing without a license.

I, for one, would rather see a class action suit, in behalf of the 360,000 or so MDs who do have licenses, directed against Dr. Denenberg and his ilk on the various boards of third party payers, including the States, such as the one recently launched by Dr. Roy Grinker, Sr. and others in Chicago. They allege that such regulation by laymen constitutes the practice of medicine without a license. Dr. Grinker informs me by phone that they have won the first round and that the case is now before a three judge federal panel. Whatever the outcome, it will undoubtedly be taken all the way to the Supreme Court, he says. If we MDs win that one, the cost of delivering medical care will once again be subordinated to the appropriateness of the care, a decision that can only be made by competent MDs who have actually seen the patient in question. Any comments?

BENJAMIN LEE, M.D.
San Francisco, Calif.

Era of Idiocy

On the assumption that at some time in the future some curious historians will deem it necessary to review the instances that won this time in our lives the label of "the era of idiocy," I wish there to be at least one recorded protest dealing with the purported need for re-licensing and recertification which has recently become so fashionable and unfortunately adopted by the hierarchy in our field of OB-GYN.

THEO. S. STASHAK, M.D.
Santa Rosa, Calif.

USSR-US Rapprochement in Cancer Pattern Seen



Prof. Nikolai Blokhin, director of the Institute of Experimental and Clinical Oncology in Moscow, as he attended a press conference sponsored by the American Cancer Society. Prof. Blokhin was in the United States to negotiate an agreement establishing a joint U.S.-U.S.S.R. cancer epidemiology program.

Continued from page 1.

patterns. He said that stomach cancer still occupies first place in morbidity in both sexes in the Soviet Union, but after peaking at about 63 cases in men and 33.5 cases in women per 100,000 population around the beginning of 1966, it has now fallen to about 55.5 in men and 27.5 in women. Though he did not cite U.S. morbidity figures, Prof. Blokhin noted that mortality from stomach cancer has been declining steadily in the United States and that among American men it was overtaken by lung cancer as a cause of death in the early 1950s.

At the same time stomach cancer has been decreasing in the Soviet Union, that of the lung has been increasing rapidly among Soviet men and less dramatically but still steadily among women in the U.S.S.R. Among Soviet men the rate has increased by almost 10 cases per 100,000 population in the last decade, the epidemiologist said.

Breast Cancer Up, Cervical Down

Prof. Blokhin, who as director of the Institute of Experimental and Clinical Oncology in Moscow is the counterpart of the director of the National Cancer Institute here, said that the incidences of female cancers in his country were also growing more like those in the United States. Cervical cancer has declined from 26 to fewer than 20 cases per 100,000 since 1965 while breast cancer has jumped from 13.7 to 17.8 cases during the same period.

Though cancer morbidity has been showing striking upward and downward shifts in the Soviet Union in recent years, Prof. Blokhin said that mortality from malignant tumors had remained fairly stable, thanks to improved screening, diagnosis, and treatment. Among men it has remained almost even at about 163 cases per 100,000 since 1961, while among women it has declined from about 102 cases to around 96 per 100,000.

"The cancer morbidity situation is very complex in my country because of its great ethnic diversity," Prof. Blokhin said. "In the Soviet Union we have 15 Soviet republics, 28 autonomous re-

publics, 8 autonomous regions, and 10 national areas. The 1970 census showed that there were more than 100 different nationalities and ethnic groups.

"Much more than in the United States, I think, these groups have tended to keep their own customs and habits, and this has affected their cancer patterns."

Esophageal cancer in both sexes is most prevalent in the Soviet Union's Middle Eastern republics—Turkmenistan, Kazakhstan, Uzbekistan, Tadzhikistan, and Azerbaïdzhân—"probably because the people there are fond of very hot tea and foods," according to Prof. Blokhin. Stomach cancer, on the other hand, is most prevalent in both sexes in the largest of the Soviet Union's components, the Russian Republic, and the Middle Eastern republics have greatly varying stomach cancer rates. And lung cancer is highest among men in the Baltic republic of Estonia but among women in the Middle Eastern Republic of Kazakhstan.

Turning to the study of cancer distribution and incidence, Prof. Blokhin said that cancer epidemiology had developed in the Soviet Union only since World War II and particularly since the early 1950s. "Before that most of our work was in diagnosis and treatment, and much emphasis was placed on animal research," he said.

The Soviet Union's cancer surveillance network is based on slightly fewer than 300 "dispensaries" scattered throughout the country. Each dispensary comprises a central cancer hospital for the area it serves, a registry of cancer patients, an epidemiological and statistical group, and a screening unit. Though the dispensaries' primary responsibility is diagnosis and treatment, they are also charged with collecting oncologic data for their areas.

Each of the 15 constituent republics of the Soviet Union has an oncology institute to oversee the work of the dispensaries in its area, and many of the republic institutes have formal cancer epidemiology departments. A Central Institute of Oncology in Leningrad belonging to the Ministry of Health co-

ordinates cancer diagnosis and treatment throughout the Soviet Union.

Prof. Blokhin's Institute in the Soviet capital, which is a unit of the U.S.S.R. Academy of Medicine rather than the Ministry of Health, is the Soviet Union's chief cancer research organization and as such coordinates oncologic studies throughout the country. Several centers with responsibility for the study of specific cancers nationwide, such as the stomach cancer unit at Vilnius, Lithuania, the breast cancer unit at Tallin, Estonia, or the gynecologic cancer unit at Tbilisi, Georgia, report to it.

5th Pact in Cancer Program

The agreement that Prof. Blokhin signed on behalf of his country with Dr. Marvin A. Schneiderman, the National Cancer Institute's associate director for field studies and statistics, is the fifth in the U.S.-U.S.S.R. cancer program, which began when President Nixon and First Secretary Leonid Brezhnev concluded a joint health studies accord in Moscow in May 1972.

Soviet and American representatives first began discussing possible joint efforts in cancer epidemiology at a

meeting in Yerevan, Armenia, in January 1974, and the meeting here between Prof. Blokhin and his six fellow Soviet investigators and NCI officials was the second in what promises to be a series.

The epidemiology agreement's most important provisions are for the compilation and publication of a joint monograph, a united breast cancer epidemiology study, and the exchange of epidemiologists between the two countries.

The monograph, to which investigators in each country will contribute half of the approximately 320 pages, will deal with epidemiologic methodology and cancer patterns in each country and will be published simultaneously in English in the United States and Russian in the Soviet Union. Prof. Blokhin predicted that it should be in draft form within a year, and translated and off the presses a year after that.

The breast cancer collaborative study is what American and Soviet researchers hope will be the first of several in cancer epidemiology, and details are to be worked out at a joint meeting later this year.

WHO Survey of 40 Countries Finds Wide Variation in Cancer Death Rates

Medical Tribune World Service

Death rates from cancer per 100,000 population vary considerably around the world, according to a survey of 40 countries conducted by the World Health Organization in 1968-69.

Scotland led in annual deaths from cancers of all types in men with 205, Chile in deaths among women with 138. The lowest rates were registered in the Dominican Republic, with 36 for men and women, and the Philippines, with 45 for men and 40 for women. The American figures were 153 and 107 for men and women respectively, placing the U.S. 18th in the world in both categories.

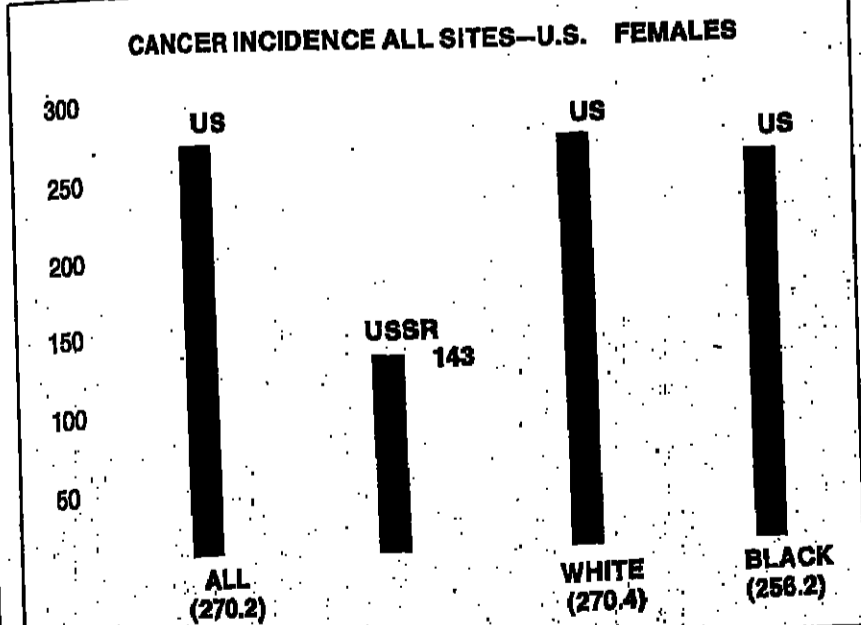
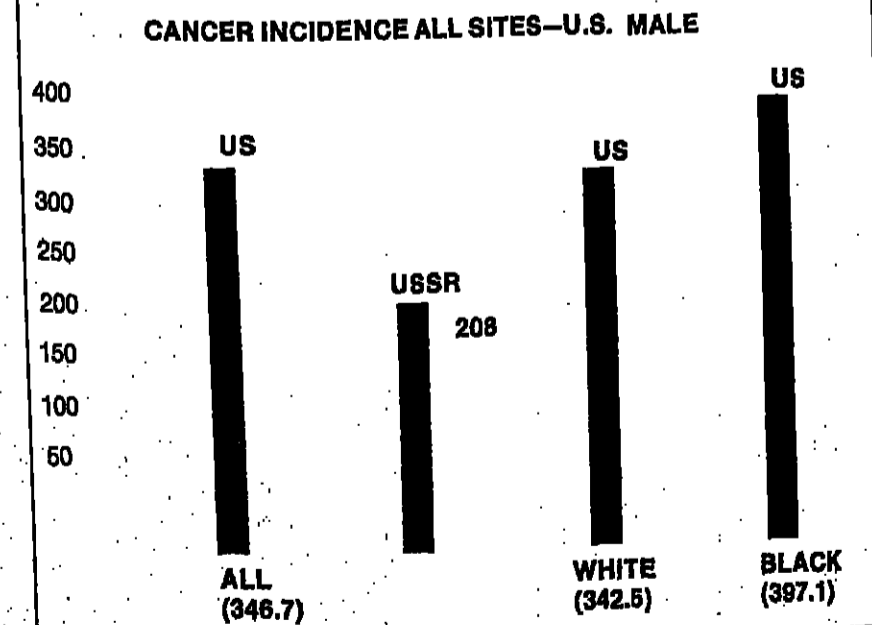
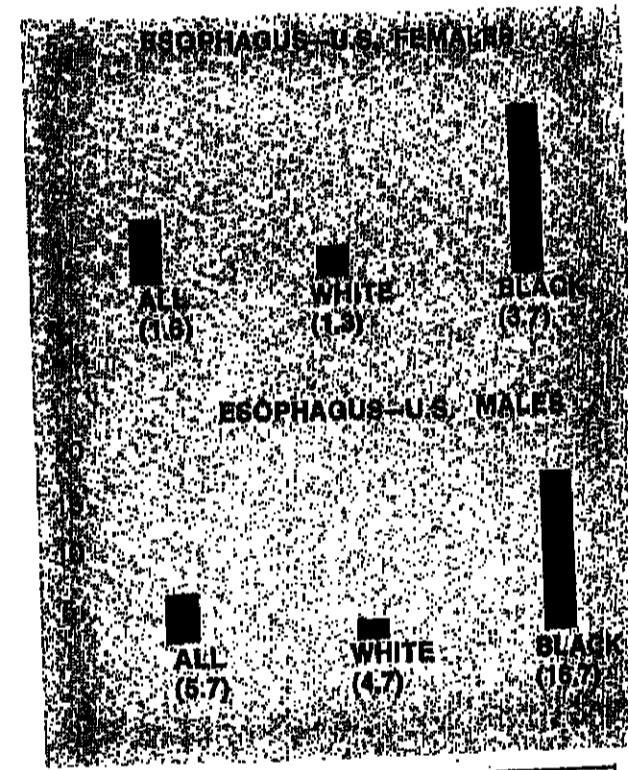
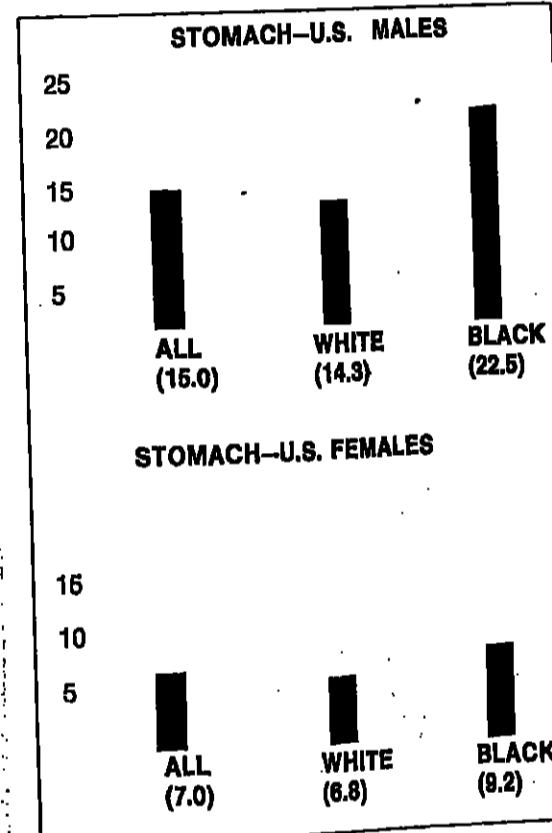
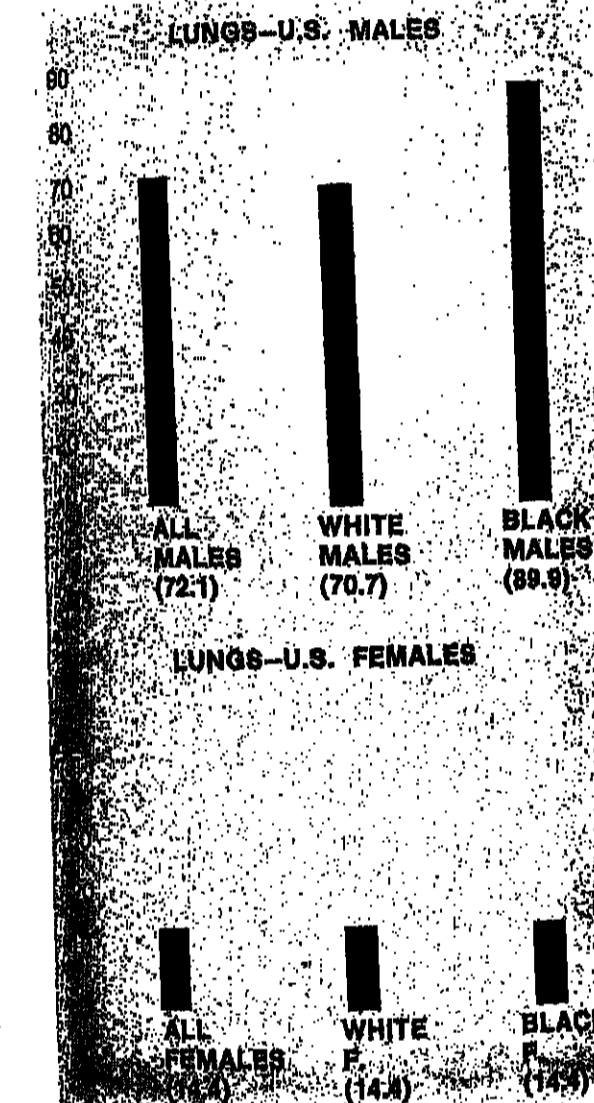
As a rule, the rate of cancer deaths among men in most countries was 30 to 60 per cent higher than for women. Only in Iceland, Mexico, and Venezuela was the rate reported among

women marginally higher than for men.

Striking differences were also noted when death rates from cancer were broken down by affected organs. In the U.S., the rate of deaths among women from breast cancer was 22 per 100,000, while for Taiwan and Japan it was 3 and 4. But Japan ranked first in deaths from stomach cancer in men (66), second among women (34). The U.S. with an incidence of fatal stomach cancers among men of 7, and women 4 per 100,000, was ranked 38th and 39th.

The range in deaths, from highest to lowest, was much wider in lung cancer (80 among Scottish males compared with 2 among Filipino women) and uterine cancer (89 in Finland, 2 in Poland), than it was from leukemia (7 in Norwegian males, less than 1 in Mauritanian females).

Cancer Incidence In US and USSR—By Site and Overall



Cancer incidence overall and by site, US-USSR compared. Annual rates per 100,000 U.S. Source: 3rd National Cancer Survey, National Cancer Institute, 1969-71. Figures are roughly, not absolutely comparable, because

standardized against different populations and age groups. The nationalized comparison is the work that is going on now at Bethesda and will go on for some time as translation etc. is carried out.

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CONTRAINDICATIONS: Anuria, hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.
WARNINGS: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte imbalance may precipitate hepatic coma. Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potential occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma. The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.
Usage in Pregnancy: Use of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. The hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.
Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hypotension, hypochloremic alkalosis, and hypokalemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea or vomiting.
Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cramps are present, or during concomitant administration of steroids or ACTH.
Interference with adequate oral intake of electrolytes may also contribute to hypokalemia. Digitalis therapy may exacerbate metabolic effects of hypokalemia especially with reference to myocardial activity.
Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Transient elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy.
Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged. Latent diabetes may become manifest during thiazide administration.
Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.
If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.
Thiazides may decrease serum PBI levels without signs of thyroid disturbance.
ADVERSE REACTIONS: Gastrointestinal—nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic), pancreatitis, cholestasis, headache, xanthopsia, vertigo, parosmia, taste perversion, dysgeusia, dermatologic—hypersensitivity—purpura, photosensitivity, rash, urticaria, necrotizing angitis, Stevens-Johnson syndrome, and other hypersensitivity reactions. Hematologic—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. Cardiovascular—orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. Other—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, reduce dosage or withdraw therapy.

DOSEAGE: Individualize dosage by titrating for maximum therapeutic response at the lowest possible dose.
Hypertension: Initial:—Usual dose 75 mg daily. **Maintenance:**—After a week dosage may be adjusted downward to as little as 25 mg or upward to as much as 100 mg daily. **Combined therapy:**—When necessary, other antihypertensives may be added gradually and with caution because of the potentiating effect of this drug. Dosages of ganglionic blockers should be halved.
Edema: Initial:—25 to 200 mg daily for several days. **Maintenance:**—25 to 100 mg daily or intermittently. Refractory patients may require up to 200 mg daily.
SUPPLIED: Tablets, 50 mg (yellow, scored), bottles of 30, 60, 100, 1000, 5000 and Accu-pak blister units of 100. Tablets, 25 mg (pink, scored); bottles of 100, 1000 and 5000.
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C I B A

One Man...and Medicine

ARTHUR M. SACKLER, M.D.
International Publisher, Medical Tribune



OF TIME AND LIFE—Part II

One Woman (of Medicine) and Art
"Her métier... writing... her language... english."

She was born in Allegheny, Pa., which is now Pittsburgh's northside, 101 years ago "of a very respectable middle class family." When she was about three years old, her family first went to Vienna and then, when she was six, moved to Paris and after a year came back to America. She was happy that her family was "reasonably poor rather than rich" and therefore had to travel to wherever her father's business would take them. They went to live in California and she who "had never read until she read English... read anything that was printed that came her way... Wordsworth, Scott and other poets, Bunyan's *Pilgrim's Progress*, Shakespeare, Burns, Congressional Records, encyclopedias, etcetera."

After she had absorbed Shakespeare, Harlow, Fielding, Smollett and Carlyle, she found herself in the agony of adolescence. Following the death of her mother and sister, she came to Baltimore, then went to Radcliffe. She early recognized that "one can only have one métier as one can only have one language. Her métier is writing and her language is english."

Student of Dr. William James

At Radcliffe she worked with Münsterberg and the most important person in her life was William James. It was in the final examination of his course that she wrote at the top of her paper, "Dear Professor James, I am so sorry but really I do not feel a bit like an examination paper in philosophy today." He gave her the highest mark. He suggested she consider philosophy or psychology and said that for the latter she must have a medical education, "a medical education opens all doors, as Oliver Wendell Holmes told me and I tell you." There was a problem. She had never intended to take a degree at college and had passed few of her entrance examinations. Things were different than now.

Studies at Johns Hopkins

After some tutoring, she entered Johns Hopkins Medical School. She liked the preclinical sciences "well enough" but for the last two years was "frankly, openly bored." The problems of examination followed her. "The big men like Halstead, Osler, etcetera knowing her reputation for original scientific work made the medical examinations merely a matter of form and passed her. But there were others who were not so amiable." She doubted she could take to the practice of medicine but might have gone into pathologic psychology but "she always says she dislikes the abnormal, it is so obvious. She says the normal is so much more simply complicated and interesting."

After a brief stay in London where she was exposed to the Beresons, the Bertrand Russells, the British Museum

Impact on American Collections

On American collections she had an impact that can only be described in terms of her own physical impression—monumental. Among many, the Cone sisters, whose collection today graces the Baltimore Museum of Art, were her intimates. Dr. Claribel Cone was a physician who studied medicine and did her graduate work in pathology and psychiatry in the United States and medical research in Germany. Together with her sister, Etta, Dr. Claribel devoted most of her life to her collecting. At one point the Cone collection of Matisse paintings and sculpture was second only to that of Dr. Barnes of Argyrol fame.

The trails of the makers of the art of the twentieth century crossed frequently at one point in Paris, at 27 rue de Fleurus. The impact of these associations radiated out in a mammoth "ripple effect" as twentieth century culture metamorphosed and attained its unique character. A few physicians were at the nodal point. But one was simultaneously part of the aesthetic wave and articulated its message; linked its disparate elements and recorded its history. She was a pioneer American intellectual adventuress who

EPIGRAMS—Clinical and Otherwise

Medicine, to produce health, has to examine disease; and music, to create harmony, must investigate discord.
Plutarch (A.D. 46-120)
Lives, Demetrius

Aspirin Kidney Damage Pronounced Hogwash



An Australian investigator feeds a pig a cake containing 56 aspirin as part of a study to determine whether aspirin causes renal damage. Previous studies showed such damage possible in rats, but rat kidneys differ in several respects from human. The study carried out by Dr. John Hobbs, of the Royal Melbourne Hospital of Australia, found no damage in pig kidneys.

never confused "the manner for the matter" and differentiated between the creators and the vulgarizers—those who were followers. She who was both creator and protagonist—was the American Woman (of Medicine) and the Arts, Gertrude Stein. The quotes are from *The Autobiography of Alice B. Toklas* by Stein.

Local Hypothermia Permits Unhurried Heart Defect Repair

Medical Tribune World Service

MONTREAL—Local cardiac hypothermia produces a bloodless, flaccid heart, which "facilitates the precise, unhurried repair of complicated intracardiac defects" and is "quite safe," Dr. John J. Lamberti, Jr., told the Society of Thoracic Surgeons meeting here.

Dr. Lamberti, now Assistant Professor of Surgery at the University of Chicago Pritzker School of Medicine, reported that the technique has been shown safe during one year's experience with 88 patients in whom "profound local cardiac hypothermia" was used during surgical correction of congenital heart defects.

The 88 patients were treated by a Harvard Medical School team at Peter Bent Brigham Hospital and Children's Hospital, Boston.

Myocardial ischemia has not been shown to harm myocardial function when protected by local cardiac hypothermia for one hour, Dr. Lamberti said.

"Successful results with cross-clamp times ranging from 90 to 120 minutes [in these 88 patients] suggest that the safe period may be much longer than is generally appreciated," he said.

"Based on this growing clinical experience," he added, "local cardiac hypothermia is employed for the protection of the myocardium in any operation which requires cross-clamping of the aorta."

Coauthors were Drs. Lawrence H. Cohn, Hillel Laks, Nina S. Braunwald, John J. Collins, Jr., and Aldo Castaneda.

Medicine on Stamps

Sun Yat-Sen



Born in 1863 in Kwantung, China, he received his M.D. from the University of Hong Kong with the first class in 1894. He began to practice medicine but his real interest was the liberation of China from the Manchu Dynasty. After the revolution of 1912 he became the first President of the Republic. After the 1921 revolution he became President of the new and independent South Chinese Republic. Exiled a year later when the republic collapsed, he died in 1925 in Peking.

Text: Dr. Joseph Kler

Stamp: Minkus Publications, Inc., New York

Abnormalities of Intestine Common in Southern India

Medical Tribune World Service

MEXICO CITY—Morphological abnormalities of the small intestine associated with malabsorption are present in from 25 to 100 per cent of the population of Southern India, as well as in other parts of the tropical world, Dr. V. I. Mathan, of Christian Medical College Hospital, Vellore, India, told the Fifth World Congress of Gastroenterology.

"It is quite common in certain areas of Southern India for total populations to be so affected," he said, "although it is not yet clear how significant for nutrition this fact may be."

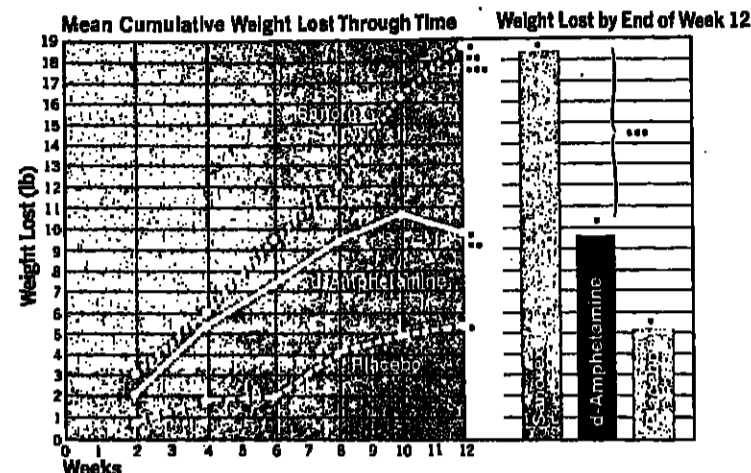
The most common cause of malabsorption in Southern India and the Caribbean, he said, is tropical sprue, which affects some 3 per cent of the population.

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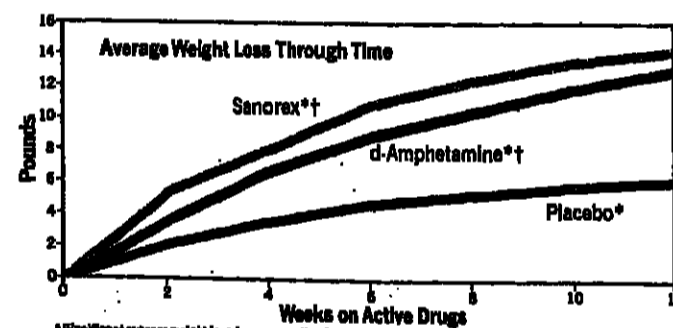
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AS EFFECTIVE AS d-AMPHETAMINE



In a double-blind study¹ of 40 obese patients (all of whom completed the study), Sanorex (1 mg t.i.d.) was more effective than either placebo or d-amphetamine (5 mg t.i.d.) in helping patients lose weight.

The 14 patients on Sanorex experienced a substantially greater mean weight loss—1½ to 2 lb/wk, as compared with 1 to 1½ lb/wk for the 14 d-amphetamine patients—throughout the 12-week phase of active medication. After the sixth week, the superiority of Sanorex became increasingly evident. And as treatment progressed, so did weight loss in patients on Sanorex—whereas after the tenth week, patients on d-amphetamine began to regain some weight.



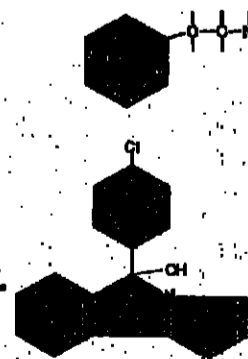
In a double-blind study² of 93 obese patients (all of whom completed the study), 30 patients received Sanorex (1 mg t.i.d.), 31 received placebo, and 32 received d-amphetamine (5 mg t.i.d.).

During the 12-week phase of active medication, patients on Sanorex lost an average of 14.1 lb, compared with 13.1 lb for d-amphetamine patients and 5.6 lb for placebo patients. Throughout the active medication phase, 63% of patients on Sanorex lost more than 1 lb/wk, compared with 38% of the d-amphetamine group and 29% of the placebo group.

BUT WITH CERTAIN DIFFERENCES

Although the pharmacologic activity of Sanorex and that of amphetamines are similar in many ways (including central nervous system stimulation in humans and animals, as well as production

Different Chemical Structure



An important chemical similarity between amphetamines and all other prescription anorexants except Sanorex is the basic phenethylamine structure to which their differentiating chemical radicals are attached.

An important chemical difference between Sanorex and all other prescription anorexants is that Sanorex is an isindole; it does not contain a phenethylamine structure.

of stereotyped behavior in animals), animal experiments suggest that there are differences. Sanorex also differs in basic chemical structure from amphetamines and all other prescription anorexants.

Different Neurochemical Action

Action of d-Amphetamine In animal studies, d-amphetamine (like intake of food) activates afferent neurons leading to appetite centers in the hypothalamus. Resulting release of norepinephrine activates the receptor neurons. Unlike food, however, d-amphetamine also suppresses norepinephrine synthesis. Thus, increasingly larger doses of d-amphetamine become necessary to produce an effect.*

Action of Sanorex (mazindol) After intake of food stimulates the release of norepinephrine from the afferent neuron, Sanorex blocks its re-uptake without disturbing normal synthesis and release.*

*The significance of these differences for humans is uncertain.

Simplicity and Flexibility of Dosage

Simple one-a-day dosage is facilitated by 2-mg tablets (taken 1 hour before lunch).
New flexibility (for the patient in whom 1 mg t.i.d. is preferred) is now facilitated by new 1-mg tablets (taken 1 hour before meals).

For Brief Summary, please see facing page.

Wednesday, April 9, 1975

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References
1. Kornhaber A. Problems and current concepts in the treatment of obesity. Scientific Exhibit presented at the New York State Academy of Family Physicians, 25th Annual Scientific Convention, McAllen, N.J., May 8-10, 1973.
2. DePalma EA, Chaykin LB, Cohen A. Double-blind clinical evaluation of mazindol, dextroamphetamine, and placebo in treatment of exogenous obesity. *Curr Ther Res* 18:355-366, July 1973.
3. Varness BJ. Practical considerations for managing obese patients: Initial interview and effecting treatment in the office. Scientific Exhibit presented at the American Medical Association, 27th Clinical Convention, Anaheim, Calif., Dec 1-4, 1973.

Indication: In exogenous obesity, as a short-term (a few weeks) adjunct in a weight reduction regimen based on caloric restriction. The limited usefulness of agents of this class should be measured against possible risk factors.

Contraindications: Glaucoma; hypersensitivity or idiosyncrasy to the drug; agitated states; history of drug abuse; during, or within 14 days following, administration of monoamine oxidase inhibitors (hypertensive crisis may result).

Warnings: Tolerance to many anorectic drugs may develop within a few weeks. If this occurs, do not exceed recommended dose, but discontinue drug. May impair ability to engage in potentially hazardous activities, such as operating machinery or driving a motor vehicle, and patient should be cautioned accordingly.

Drug Interactions: May decrease the hypotensive effect of guanethidine; patients should be monitored accordingly. May markedly potentiate pressor effect of exogenous catecholamines; if a patient is recently taking mazindol must be given pressor amine agents (e.g., levaterenol or isoproterenol) for shock (e.g., from a myocardial infarction), extreme care should be taken in monitoring blood pressure at frequent intervals and initiating pressor therapy with a low initial dose and careful titration.

Drug Dependence: Mazindol shares important pharmacologic properties with amphetamines and related stimulant drugs that have been extensively abused and can produce tolerance and severe psychological dependence. Manifestations of chronic overdosage or withdrawal with mazindol have not been determined in humans. Abstinence effects have been observed in dogs after abrupt cessation for prolonged periods.

There was some self-administration of the drug in monkeys. EEG studies and "liking" scores in human subjects yielded equivocal results. While the abuse potential of mazindol has not been further defined, possibility of dependence should be kept in mind when evaluating the desirability of including the drug in a weight-reduction program.

Use in Pregnancy: In rats and rabbits an increase in neonatal mortality and a possible increased incidence of rib anomalies in rats were observed at relatively high doses. Although these studies have not indicated important adverse effects, the use of mazindol in pregnancy or in women who may become pregnant requires that potential benefit be weighed against possible hazard to mother and infant.

Use in Children: Not recommended for use in children under 12 years of age. **Precautions:** Insulin requirements in diabetes mellitus may be altered. Smallest amount of mazindol feasible should be prescribed or dispensed at one time to minimize possibility of overdosage. Use cautiously in hypertension, with monitoring of blood pressure; not recommended in severe hypertension or in symptomatic cardiovascular disease including arrhythmias, mouth, tachycardia, constipation, nervousness, and insomnia. **Cardiovascular:** Palpitation, tachycardia. **Central Nervous System:** Overstimulation, restlessness, dizziness, insomnia, dysphoria, tremor, headache, depression, drowsiness, weakness. **Gastrointestinal:** Dryness of mouth, unpleasant taste, diarrhea, constipation, nausea, other gastrointestinal disturbances. **Skin:** Rash, excessive sweating, clamminess. **Endocrine:** Impotence, changes in libido have rarely been observed. **Eyes:** Long-term treatment with high doses in dogs resulted in some corneal opacities, reversible on cessation of medication; no such effect has been observed in humans. **Dosage and Administration:** 1 mg three times daily, one hour before meals, or 2 mg per day, taken one hour before lunch in a single dose.

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Big Hurdles to Development Of Syphilis Vaccine Persist

By JOHN P. HENAHAN
Special Tribune Correspondent

LOS ANGELES—Nine years after it was first shown that rabbits could be protected against syphilis with massive injections of *Treponema pallidum*, major obstacles to the development of a vaccine for human use still persist.

In spite of recent successes in preserving inactivated *T. pallidum* at low temperature and experimental indications that the syphilis-causing organism will survive in tissue culture, large scale production of highly purified *T. pallidum* micro-organisms for potential use as a human vaccine have proved fruitless, Dr. James Miller told the 104th Annual Session of the California Medical Association here. Dr. Miller is director, Treponemal Research Laboratory, U.C.L.A. School of Medicine.

One of the most frustrating problems is separating the *T. pallidum* organisms from the rabbit testicular tissue in which they are most frequently propagated in vivo, he said. Use of the tissue-contaminated organisms in humans, he explained, could lead to allergic reactions, testicular atrophy, and sterility.

Long Storage Possible

On the positive side, the U.C.L.A. investigators have shown that radiation-inactivated *T. pallidum* stored in liquid nitrogen remain "morphologically and immunogenetically intact" for at least 18 months. Storage of a vaccine for long periods of time is necessary for practical use in human beings, he said.

In addition, Dr. Miller's group has shown that intravenous and intramuscular injection of the stored micro-organisms protected rabbits against infection or delayed the onset of experimental syphilis.

"Three weeks after the last immunizing injection, the vaccinated animals were challenged intradermally at each of four sites with 1500 virulent *T. pallidum* per site. Eight of the nine animals immunized by the intravenous route showed a significant delay in the

development of lesions, ranging from six to nine days after the average incubation period of 11 days in non-immunized controls.

"Each of the eight animals immunized by the intramuscular route also exhibited a significant delay in the development of lesions. Thus, the experiment clearly shows that some degree of homologous acquired resistance develops as a result of intravenous and intramuscular vaccination with liquid nitrogen-preserved [organisms], employing a practical time schedule."

Faster Immunity Sought

In 1965, when Dr. Miller first showed that rabbits could be successfully immunized against syphilis, he injected a total of 3.7 billion *T. pallidum* cells in 60 intravenous injections over a 37 week period. In studies now underway at U.C.L.A., 16 billion micro-organisms will be administered over a 16 week period in hopes of developing immunity more rapidly. They also believe that a suspension of the "vaccine" in an alginate-glucanate adjuvant should increase its effectiveness.

As for growing larger quantities of purified *T. pallidum*, Dr. Miller—in collaboration with Dr. John Sykes of the Southern California Cancer Center—has recently begun an N.I.H.-supported study aimed at the in vitro cultivation of the microorganism in monolayered cultures of rabbit testicular cells as well as in a human tumor cell line. Although the in vitro growth of *T. pallidum* has previously been impossible, for as yet unknown reasons, Dr. Miller is encouraged by the recent discovery in his lab that the microorganism will enter and survive in rabbit testicular cells in vitro for periods as long as four days.

"I am hopeful, I can't predict when this will happen, but I do feel that some time in the future, but not before five years, we're going to have a syphilis vaccine for human beings."

"Exciting experiments designed to determine those factors necessary to allow their growth and multiplication are continuing," he said.

Major Complications Absent In Trials With Falope Ring

Continued from page 1

instrument's insertion into the pelvic cavity.

"On location of the fallopian tubes, the grasping forceps is employed to pick up one of the tubes, one to two inches from the cornu of the uterus," Dr. Yoon stated.

The tube is pulled into the cylinder to form a knuckle, he said, and then one or two rings are slipped over the segment. The same procedure is followed for both fallopian tubes.

The section of the fallopian tube enclosed within the ring either develops a scar or degenerates and is removed by metabolic processes, Dr. Yoon explained. The rest of the tube remains unaltered.

The only complications so far, Dr. Yoon reported, have been the occa-

sional tearing of a fallopian tube when grasping it with the forceps and, in some cases, "significant lower abdominal pain requiring medication with non-narcotic analgesics in the first two post-operative days."

Since this may be due to the "avascular necrosis of the contained segment," Dr. Yoon suggested that rings may be impregnated with a local anesthetic in the future.

So far, no pregnancies have occurred among these women, Dr. Yoon said, but he pointed out that one-year failure rates for the procedure will not be available until October, 1976.

Also involved in the project are Drs. Clifford R. Wheelless, Jr., and Theodore M. King, of Hopkins' Department of Gynecology and Obstetrics.

Skating Without Snow



Dr. John Stephens, of Stanford University, "roller-skis" around the campus to exercise and prepare for cross-country skiing. The roller skis are a common sight in Europe but not well known in this country.

Mayo Study Finds No Breast Cancer Link to Rauwolfia

Continued from page 1

tis and cholelithiasis, hypertensive therapy included a rauwolfia product in 40 patients (8.9 per cent), while among the breast cancer patients, 30 patients (7.6 per cent) had received rauwolfia as part of a hypertensive regimen.

Hypertension was a very frequent associated finding, more so in the gall bladder disease controls (48.4 per cent) than in women with breast cancer (37.0 per cent). In both groups, elevated blood pressure had been treated in over 60 per cent of the patients.

Dr. O'Fallon concluded that it would be unwarranted to alter antihypertension regimens which include rauwolfia in the absence of a demonstration of an association of possible cancer risk with the therapeutic agent.

Additional studies are in progress at the Mayo Clinic, including a follow-up of 2,500 hypertensive females observed at the Mayo Clinic in the period of 1950-64.

Conclusions Support Edwards

The conclusions of the Mayo group support the earlier recommendations of Dr. Charles C. Edwards, former Assistant Secretary of Health, who stated (MT, Oct. 23, 1974) that a "preliminary review by a committee of representatives of leading medical institutes and sections of HEW has led... to the definitive recommendation that there 'should be no general change or disruption of therapy in patients with high blood pressure' until definitive conclusions are possible."

Dr. O'Fallon is on leave from Duke University School of Medicine, where he is Associate Professor of Community Health Sciences. Coauthors were Drs. D. R. Labarthe, L. T. Kurland and W. F. Taylor.

Exceptionally well absorbed oral broad spectrum antibiotic may be taken with meals

Larocin® (amoxicillin) achieves high blood and urine levels

Low incidence of diarrhea to date in clinical studies

NUTLEY, N.J.—Roche Laboratories recently introduced an oral broad spectrum antibiotic: Larocin (amoxicillin). Larocin represents a significant contribution to antibacterial chemotherapy, one which will perform effectively in the treatment of a wide range of infections due to susceptible organisms (see chart at right).

Absorption called the key

The key pharmacologic characteristic of Larocin (amoxicillin) is its rapid and efficient absorption from the gastrointestinal tract. Not only is it stable in stomach acid, but the presence of food has no significant effect on the antibiotic's absorption. Thus Larocin may be taken by patients on a convenient t.i.d. schedule without regard to meals. The reconstituted oral suspension and pediatric drops may be added to liquids such as formula, milk, fruit juice or soft drinks for easy administration to small children.

Because of its efficient absorption characteristics, high blood and urine levels of Larocin (amoxicillin) are rapidly achieved. Peak serum levels average 4.2 mcg/ml two hours after a single 250-mg oral dose and 7.5 mcg/ml one hour after a single 500-mg oral dose—both levels approximately twice as high as those obtained with equal doses of ampicillin.^{1,2}

On a multiple-dose regimen, when given every eight hours for 3 days, the lowest mean serum levels of Larocin approximated 1.0 mcg/ml after 250 mg and 1.25 mcg/ml after 500 mg.³ Although the therapeutic range of blood levels for the penicillins is not well established, these results demonstrate that blood levels may be expected to remain above the MIC's for all of the nonurinary pathogens susceptible to Larocin when it is administered at clinically recommended doses (see chart below).

Most of Larocin is excreted unchanged in the urine.⁴ Average urinary excretion within 6 to 8 hours after oral administration ranges from 40 to 79% for the 250-mg dose and 59 to 79% for the 500-mg dose.^{1,5}

1. Croydon EAP, Sutherland R: *Antimicrob Agents Chemother*—1970, pp. 427-430. 2. Neu HC, Winshell EB: *Antimicrob Agents Chemother*—1970, pp. 428-429. 3. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey. 4. Leigh DA: *Curr Med Res Opin* 7:10-13, 1972. 5. Boday GP, Nance J: *Antimicrob Agents Chemother* 1:388-392, 1972.

Hypersensitivity reactions can occur

As with other penicillins, it is anticipated that adverse reactions to Larocin (amoxicillin) will be largely limited to sensitivity phenomena. While anaphylaxis is rare in patients treated with oral

GRAM-POSITIVE	
Alpha-hemolytic streptococci	
Beta-hemolytic streptococci	
<i>Streptococcus faecalis</i>	
<i>Diplococcus pneumoniae</i>	
Nonpenicillinase-producing staphylococci	
GRAM-NEGATIVE	
<i>Hemophilus influenzae</i>	
<i>Escherichia coli</i>	
<i>Proteus mirabilis</i>	
<i>Neisseria gonorrhoeae</i>	

In vitro bactericidal activity

Note: Because Larocin (amoxicillin) does not resist destruction by penicillinase, it is not effective against penicillinase-producing bacteria such as resistant staphylococci. All strains of *Pseudomonas* and most strains of *Klebsiella* and *Enterobacter* are resistant.

penicillins, the possibility must nevertheless be kept in mind. Larocin is contraindicated in patients with a history of penicillin hypersensitivity. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT (See Warnings section of complete product information, a summary of which appears at right.)

Efficacy demonstrated in many infections

Amoxicillin has been administered successfully to patients with a wide range of commonly seen infections due to susceptible organisms.* Over-all clinical evaluation of amoxicillin therapy was considered a "success" or "improvement" in 1267 of 1850 evaluable cases (93.8%).†

Agas of the 1850 patients studied ranged from under one year to over 80 years. Larocin capsules were administered to 800 patients and oral suspension to the remaining 550. Dosage of the capsules ranged from 250 mg t.i.d. (the most frequently used dosage) to a single 8-Gm dose for the treatment of acute uncomplicated gonorrhea. Dosage of the oral suspension ranged from 50 mg t.i.d. to 250 mg t.i.d., with 125 mg t.i.d. the most frequent. The majority of patients were treated from seven to 10 days. A breakdown by type of infection follows:

Otitis Media: The pathogens most commonly isolated were *Diplococcus pneumoniae* and *Haemophilus influenzae*. Of 130 cases with this diagnosis, 127 (98%) were rated as a "success" or "improvement" after treatment with Larocin (amoxicillin).

Streptococcal Sore Throat: A success rate of 86% (174 of 202 cases) was observed with Larocin against the responsible pathogen, beta-hemolytic streptococci. The great majority of the 202 patients in this group were children who received the oral suspension.

Other Upper Respiratory Infections: Beta-hemolytic streptococci were the offending organisms for most of the infections in this group, which were diagnosed primarily as pharyngitis, with some cases of tonsillitis and a few cases of sinusitis. A success rate of 82% (56 of 68 cases) was achieved with Larocin.

Lower Respiratory Infections: Treatment with Larocin resulted in "success" or "improvement" in all of the 52 cases in which *Diplococcus pneumoniae* was cultured. *Staphylococcus aureus* was also cultured in 26 of the 98 cases; Larocin showed "success" or "improvement" in 96% (25 of 26 cases). The most common clinical conditions were bronchitis and bronchopneumonia.

Urinary Tract Infections: Cystitis, pyelonephritis and asymptomatic bacteriuria were the most frequent clinical diagnoses in this group. Of the 404 cases evaluated, *Escherichia coli* was cultured in 306 cases and treatment with Larocin resulted in "success" or "improvement" in 284 cases (93%). *Proteus mirabilis* was cultured in 70 patients, with Larocin effective in 67 (96%).

Skin and Soft Tissue Infections: *Staphylococcus aureus* was cultured in 108 cases, with "success" or "improvement" in 104 (96%); while beta-hemolytic streptococci were cultured in 99 cases, with "success" in 97 (98%). Impetigo and abscess were the most frequent diagnoses.

Gonorrhea: Administered as a single 8-Gm oral dose, Larocin showed a success rate of 97% in both males (85 of 88 cases) and females (114 of 118 cases).

*Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110. †"Success" or "improvement" was determined by a combination of clinical and bacteriological criteria. Infections due to beta-hemolytic streptococci and *N. gonorrhoeae* only successes were included.

Low incidence of side effects reported to date

During the clinical investigations with amoxicillin, all cases treated were evaluated for side effects. No side effects or laboratory abnormalities which would be considered unusual for a penicillin derivative were reported by any of the investigators.

In 2658 total courses of therapy with amoxicillin, therapy was discontinued in only 52 patients

Drug-Related Side Effects Associated with Amoxicillin

Based upon 8658 courses of therapy: 1811 with the capsules and 847 with the oral suspension.

SIDE EFFECT	CAPSULES		SUSPENSION	
	#	%	#	%
Diarrhea	24	1.3	18	2.1
Rash	24	1.3	17	2.0
Nausea	7	0.3	1	0.1
Urticaria	8	0.4	2	0.2
Moniliasis	7	0.3		
Nausea/Vomiting	4	0.2		
Diarrhea/Nausea	3	0.1		
Vomiting	2	0.1	4	0.4
Dizziness	2	0.1		
Nausea/Headache	2	0.1		
Rash/Urticaria	2	0.1	1	0.1
Esophageal Spasm	1	0.05	1	0.1
Stomachache	1	0.05		
Belching	1	0.05		
Drowsiness	1	0.05		
Belching/Itching	1	0.05		
Fever/Itching	1	0.05		
Difficult Breathing	1	0.05		
Mucus in Pharynx	1	0.05		
Diarrhea/Urticaria	1	0.05	4	0.4
Diarrhea/Vomiting	1	0.05		
Dizziness/Headache	1	0.05		
Conjunctival Erythema	1	0.05		
G.I. Bleeding	1	0.05		
Abdominal Cramps	1	0.05	1	0.1
Diarrhea/Rash	1	0.05	1	0.1
Rash/Diarrhea/Vomiting	1	0.05	1	0.1
Sore Tongue	1	0.05	1	0.1
Rash/Vomiting	1	0.05		
TOTAL	102	5.6	52	6.1

(1.9%) because of drug-related side effects. Laboratory abnormalities possibly related to amoxicillin occurred infrequently.

In these studies, there was a low incidence of diarrhea reported with amoxicillin capsules—1.7% or 30 of 1811 patients. Especially noteworthy was the low incidence of diarrhea reported with amoxicillin oral suspension—only 2.8% or 24 of 847 patients, significantly less ($p < 0.05$) than the incidence of diarrhea with ampicillin oral suspension (5.3% or 15 of 282 patients).

In breaking down the over-all incidence of diarrhea by age groups, it was found that in the group from 0 to 1 (newborn and 1-year-old infants), 18 of 108 patients receiving amoxicillin oral

suspension developed diarrhea, for an incidence of 12%. This represents over one-half the total number of diarrhea cases seen in the 847 patients treated with amoxicillin oral suspension.

Throughout each of the remaining age categories, starting from age 2 to 10 and in the general grouping from age 11 to 20, the incidence of diarrhea in patients treated with amoxicillin oral suspension ranges from 2% down to 0 in the older groups. There were few cases of diarrhea beyond the age of six.

The incidence of diarrhea with Larocin (amoxicillin) can therefore be expected to be considerably higher in the newborn and infant age groups than in older children, which is true of all antibiotics.

Usual Adult and Pediatric Dosages

INDICATION	STRAIN ISOLATED	ADULT DOSAGE	PEDIATRIC DOSAGE*
Infections of the ear, nose, throat	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, <i>H. influenzae</i>	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Infections of the lower respiratory tract	Streptococci, pneumococci, nonpenicillinase-producing staphylococci, <i>H. influenzae</i>	500 mg t.i.d.	Oral Suspension: 40 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 1 ml t.i.d.; 6-8 kg (13-18 lbs): 2 ml t.i.d.
Infections of the genitourinary tract	<i>E. coli</i> , <i>Proteus mirabilis</i> , <i>Strep. faecalis</i>	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Infections of the skin and soft tissues	Streptococci, susceptible staphylococci and <i>E. coli</i>	250 mg t.i.d.	Oral Suspension: 20 mg/kg/day in divided doses t.i.d. Drops: Under 6 kg (13 lbs): 0.5 ml t.i.d.; 6-8 kg (13-18 lbs): 1 ml t.i.d.
Severe infections, or infections caused by less susceptible organisms		500 mg t.i.d.	Oral Suspension: 40 mg/kg/day in divided doses t.i.d.
Gonorrhea, acute uncomplicated	<i>N. gonorrhoeae</i>	3 grams—single oral dose	

*Note: Children weighing more than 8 kg (18 lbs) should receive the appropriate dose of the Oral Suspension: 125 mg or 250 mg/5 ml. Children weighing more than 20 kg should be dosed according to adult recommendations.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Infections due to susceptible strains of the following gram-negative organisms: *H. influenzae*, *E. coli*, *P. mirabilis* and *N. gonorrhoeae*; and gram-positive organisms: streptococci (including *Streptococcus faecalis*), *D. pneumoniae* and nonpenicillinase-producing staphylococci. Therapy may be instituted prior to obtaining results from bacteriological and susceptibility studies to determine causative organisms and susceptibility to amoxicillin.

Contraindications: In individuals with history of allergic reaction to penicillins.

WARNINGS: SERIOUS AND OCCASIONALLY FATAL HYPERSENSITIVITY (ANAPHYLACTOID) REACTIONS REPORTED IN PATIENTS ON PENICILLIN THERAPY. ALTHOUGH MORE FREQUENT FOLLOWING PARENTERAL THERAPY, ANAPHYLAXIS HAS OCCURRED IN PATIENTS ON ORAL PENICILLINS. MORE LIKELY IN INDIVIDUALS WITH HISTORY OF SENSITIVITY TO MULTIPLE ALLERGENS. BEFORE THERAPY, INQUIRE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO PENICILLINS, CEPHALOSPORINS OR OTHER ALLERGENS. IF ALLERGIC REACTION OCCURS, INSTANTLY DISCONTINUE THERAPY AND CONSIDER DISCONTINUANCE OF AMOXICILLIN. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPI-NEPHRINE, ADMINISTER OXYGEN, INTRAVENOUS STEROIDS AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, AS INDICATED.

Usage in Pregnancy: Safety in pregnancy not established.

Precautions: As with any potent drug, assess renal, hepatic and hematopoietic function periodically during prolonged therapy. Keep in mind possibility of superinfections with mycotic or bacterial pathogens; if they occur, discontinue drug and/or institute appropriate therapy.

Adverse Reactions: As with other penicillins, untoward reactions will likely be essentially limited to sensitivity phenomena and more likely occur in individuals previously demonstrating penicillin hypersensitivity and those with history of allergy, asthma, hay fever or urticaria. Adverse reactions reported as associated with use of penicillins: Gastrointestinal: Nausea, vomiting, diarrhea. **Hypersensitivity Reactions:** Erythematous maculopapular rashes, urticaria. **NOTE:** Urticaria, other skin rashes and

serum sickness-like reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Discontinue amoxicillin unless condition is believed to be life-threatening and amenable only to amoxicillin therapy. **Liver:** Moderate rise in SGOT noted, but significance unknown. **Hemic and Lymphatic Systems:** Anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia, agranulocytosis. All are usually reversible on discontinuation of therapy and believed to be hypersensitivity phenomena.

Dosage: Ear, nose, throat, genitourinary tract, skin and soft tissue infections—Adults: 250 mg every 8 hours. Children: 20 mg/kg/day in divided doses every 8 hours; under 6 kg, 0.5 ml of Pediatric Drops every 8 hours; 6-8 kg, 1 ml of Pediatric Drops every 8 hours. **Lower respiratory tract infections and severe infections or those caused by less susceptible organisms—Adults:** 500 mg every 8 hours. Children: 40 mg/kg/day in divided doses every 8 hours; under 6 kg, 1 ml of Pediatric Drops every 8 hours; 6-8 kg, 2 ml of Pediatric Drops every 8 hours. **Gonorrhea** (acute uncomplicated anogenital and urethral infections)—Males and females: 3 grams as a single oral dose. **NOTE:** Children weighing more than 8 kg should receive appropriate dose of oral suspension 125 mg or 250 mg/5 ml. Children weighing 20 kg or more should be dosed according to adult recommendations.

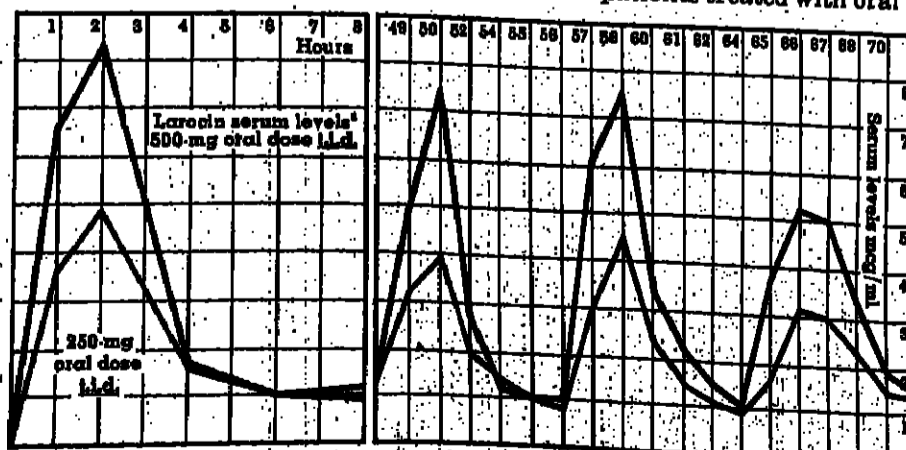
Note: In gonorrhea with suspected lesion of syphilis, perform dark-field examinations before amoxicillin therapy and monthly serological tests for at least four months. In chronic urinary tract infections, frequent bacteriological and clinical appraisals are necessary. Smaller than recommended doses should not be used. In stubborn infections, several weeks' therapy may be required. Except for gonorrhea, continue treatment for a minimum of 48-72 hours after patient is asymptomatic or bacterial eradication is evidenced. Treat hemolytic streptococcal infections for at least 10 days to prevent acute rheumatic fever or glomerulonephritis.

Supplied: Amoxicillin as the trihydrate: Capsules, 250 mg and 500 mg; oral suspension, 125 mg/5 ml and 250 mg/5 ml; pediatric drops, 50 mg/ml.

Larocin® (amoxicillin)

an important contribution
to oral broad spectrum
antibiotic therapy

ROCHE



Prosthesis Corrects a Rare Aortic Stenosis

By SUE WYMELENBERG
Special Tribune Correspondent

BOSTON—A prosthesis that corrects a rare form of congenital aortic stenosis has been developed by the cardiovascular research team at Children's Hospital Medical Center and Thermo Electron Corporation here.

Its successful use was briefly outlined by Dr. John F. Keane at the recent American College of Cardiology meeting in Houston and described more fully by Dr. C. Grant LaFarge at a press conference at the hospital.

The prognosis for diffuse supra-aortic stenosis usually is a poor one because replacement of the aortic valve with a conventional prosthesis is not feasible when the annulus as well as the aorta is severely underdeveloped.

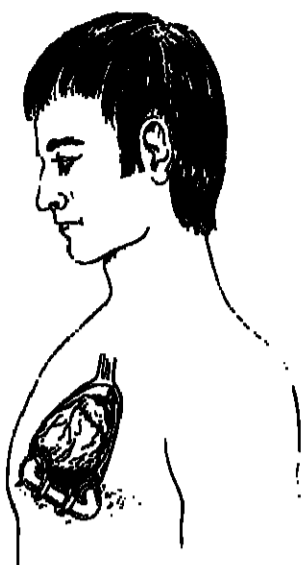
Patient Resumes Activities

Implanted in a 23-year-old man whose condition had been steadily worsening since his teens—he had been confined to a wheelchair for several years—a U-shaped shunt was interposed between the left ventricular apex and the descending thoracic aorta, bypassing the obstructed area.

The patient is now able to walk and climb stairs, and has resumed his education and some sports activities.

The prosthesis is composed of a Hancock Dacron graft, containing an aortic valve from a pig, coupled to stainless steel tubing coated with polyurethane and lined with flocked polyester fibrils.

Different lengths of the tubing combined with flexible elbow joints make the device non-kinking but "highly adjustable," Dr. LaFarge said, "so that it



U-shaped prosthesis developed at Children's Hospital, Boston, for use in diffuse supra-aortic stenosis consists of Hancock Dacron graft containing pig aortic valve coupled to stainless-steel tubes lined with Dacron fibrils. Pig valve, preserved in glutaraldehyde, is expected to remain flexible 10 years.

can be tailored to fit the individual patient." For this patient, the device was 7 cm. wide and 9.5 cm. long.

A spin-off from an ongoing effort at the medical center's Cardiovascular Research Laboratory to develop an implantable, mechanical blood pump, the metal surfaces in the shunt are coated with the Dacron fibrils because the investigators have found these encourage the growth of a fine layer of fibrin and blood cells.

From this there gradually develops a pseudo-endothelium of fibrocytes,

which in animal studies at the laboratory has proved compatible with blood flow for a long period of time.

Because the porcine valve had been preserved in glutaraldehyde, it is expected to maintain its flexibility for at least 10 years, the investigators said.

The Dacron portion of the shunt is anastomosed to the side of the aorta and the inflow end of the tubing is inserted into the apex of the left ventricle. The body of the prosthesis is sutured to the diaphragm for support and stability. The actual implantation in this patient took 45 minutes.

14 Patients Seen in 19 Years

The patient was one of 14 seen over a period of 19 years who had an obstruction above the aortic valve. Nine had a discrete area of stenosis which was relieved by enlarging the stenosed area with a Dacron patch.

In the remaining five, the hypoplasia was diffuse and involved the annulus and ascending aorta. Three patients died because it was impossible to repair the defect. A fifth patient is being evaluated to see whether the shunt can be applied.

Although this congenital abnormality is rare, Dr. LaFarge said that "conservatively speaking, there are at least 100 cases currently in medical centers in the United States, and some cardiologists put that figure between 300 and 500."

Dr. William F. Bernhard performed the surgery. Other members of the team that developed the shunt include James Carr, Sylvia Fricze, and Nancy Cole, laboratory staff members, and Vincent Poirier of Thermo Electron.

Drastic NY Malpractice Overhaul Proposed

Continued from page 1

chairman of the state medical society's subcommittee on Malpractice, told MEDICAL TRIBUNE.

The set of proposals approved by the society's House of Delegates and presented to Gov. Hugh Carey and the state legislature, was outlined by Dr. Patterson and Dr. John H. Carter, Clinical Professor of Surgery at Albany Medical Center and chairman of the legislative Committee of the Medical Society. It includes:

Jury System Replacement

- The creation of a "Patients' Indemnification Board" to replace the jury system in malpractice suits, and of "Hearing Panels" to give preliminary judgments on all actions and dismiss them if the panel votes unanimously that the action is "frivolous." The Board would be made up of four physicians, four lawyers, and four laymen, all appointed by the governor, while the panels, located in each of the state's judicial districts, would consist of one physician, one lawyer and one layman.
- A stricter statute of limitations on malpractice liability. Claims for birth injuries could only be brought until the patient was six years of age, instead of the present 21. Limitations on other claims would be dated from day of occurrence of alleged malpractice, rather than day of discovery, and in no case more than three years.

- Dollar claims and awards to be held in confidence and not publicized in news media.

- Suits to be placed on court dockets and heard by panels within forty-five days of a summons being served on the defendant physician.

- No duplication of indemnification in malpractice awards for patients' loss of income, when such loss is wholly or partially reimbursed by other insurance policies or unemployment compensation.

- A legal definition of malpractice as that which is "deviant from usual standards in the community in which it was performed." In order to win any award, the claimant would have to prove such deviation, and show that it resulted directly in injuries that would not have otherwise occurred. Expert testimony in this regard would only be heard from board-certified specialists licensed in New York. At present, according to Dr. Patterson, malpractice is "virtually undefined and thus unlimited," and "unfortunately, we have colleagues, some of them not even licensed in New York, who show up to testify in front of juries, one week as gynecologists, the next as neurosurgeons, the next perhaps as cardiologists."

- Substantial transfer of authority and responsibility for disciplining physicians from the state boards of Education and Regents, to the medical pro-

fession, specifically the Committee on Professional Conduct of the State Board of Medicine. "We know there are some few doctors out there who should be disciplined—we know it better than the Board of Regents," Dr. Patterson said. "But as matters stand now, it takes forever for a doctor to be suspended or have his license revoked. The machinery for dealing with misconduct is too slow and cumbersome. And all that physicians can do now is throw someone out of the medical society, which is worse than doing nothing."

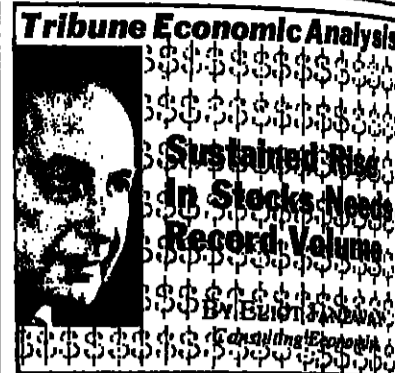
'Informed Consent' Change

- Lack of "informed consent" to be abolished as grounds for malpractice claim, except in cosmetic and experimental procedures.

- Awards to be fixed by the Patients' Indemnification Board, and attorney's fees to be based on a sliding scale, with the percentage of the fee decreasing as the amount of the award increases.

Dr. Carter said he realized some of these proposals entailed major revision of law, and one—for the Indemnification Board to replace juries—might be unpopular and require a Constitutional Amendment. But he said that the situation was so critical that only radical changes would help.

"If we can clear away the emotionalism and publicity from the problem,



A simple and familiar word sums up the confrontation the market has run itself into: ultimatum. Either it will set new records for the volume of shares traded per day, or it won't.

Before the market took off, the theory that the volume of daily trading determines the prices at which stocks are traded was just a theory. The move from under 600 on the Dow to over 750 has transformed this calculation into a condition. The volume needed to keep the market moving is readily reducible to a count. The dividing line between hope and fear is delineated by the volume level of 25,000,000 shares traded per day.

Not even 35,000,000-share days are any longer enough for sustained advances.

Expectation is the mother of market performance. Surprises are the catalysts of big moves. But the present Wall Street focus on the volume needs of the 1975 rally is making a well-hedged and open-minded provision for a surprise in either direction. The market-makers would be surprised to see the trading pace stepped up to 40,000,000 shares a day; they would be even more surprised to see it hold there. But they would not be surprised to see the Dow Jones Average lead the rest of the market back to and even through the magic mark of 1,000 on such sustained volume.

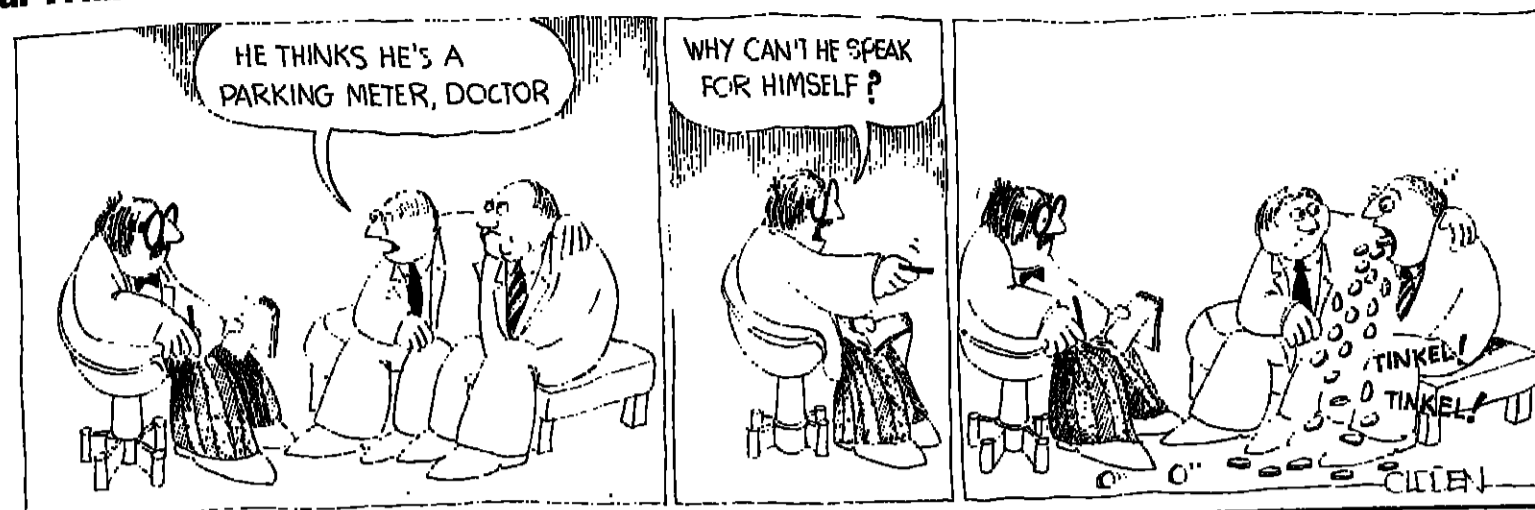
The same pragmatic test now counts the 35,000,000-share volume level as unlikely to sustain either prices or volume. It figures that a slowdown under 25,000,000 shares is probable. And far from being surprised by another price slump following a volume slowdown, the market-makers rate this sequence a cinch.

and streamline and rationalize the legal machinery, we just may be able to hold the line on cost or even bring them down. If we can't control costs, there's not much hope."

He reiterated the Medical Society's opposition to both a joint underwriter's system pooling the resources of various private companies, which has passed the state senate, and a compulsory state insurance fund. "Neither would control costs," he maintained.

"Provided meaningful legislative change is achieved by passage of a good number of our proposals soon, we are prepared to insure ourselves. Our House of Delegates has already approved the formation of a mutual insurance company that would build its reserve from an initial assessment. It would be non-profit and would handle only malpractice. Of course, this would not prevent private companies from competing, once writing malpractice insurance becomes economically sensible again."

Clinical Trials



TRIBUNE SPORTS REPORT

Better Records Urged to Arm Team MDs for Legal Battles

Medical Tribune Report

CLEVELAND—"You're going to have to keep better records than ever before," Dr. Victor Ippolito, 30-year veteran physician to the Cleveland Browns professional football team, told physicians, coaches, and trainers at a sports symposium here at the Cleveland Clinic.

"This is not only good for the athlete, but it's good for you, too," he said, since the malpractice crisis has hit the professional sports level.

"We're hearing of lawsuits for a million dollars. One man is being sued for \$7,000,000. As salaries go up in professional sports, more of these players are going to sue the doctors if they can't play. So this means that physicians and trainers both have to practice the best way they can."

Not Just at Pro Level

The current popularity of lawsuits for alleged malpractice is not going to be confined to the professional level, Dr. Ippolito added. Team doctors for high-school and college teams too, had "better make sure that every injury is recorded."

All team physicians should also perform much more thorough physical examinations than many have been doing, he advised. On the Browns, as a start, every player undergoes an examination that is "the most complete in all of professional sports," he said. It includes an SMA-12, pulmonary function studies, x-rays, and in the case of some of the older players, stress testing. No player is allowed to go out on the field for the first practice until all of these tests are checked out.

"You find some of these big football players would like to skip the blood tests, but we don't let them," said Dr. Ippolito. "Each player gets a card telling him what studies are to be done, and where to go, and each section of that card must be okayed. We've got a team of 27 people assembled, including physicians, nurses, and technicians, and we get 50 physicals done in four hours. That includes the coaches and the trainers. We do some of the physicals on one Sunday and the rest on the next Sunday."

If this is the player's first exam, he said, a complete history is taken and

the player initials it. Otherwise, the history is updated.

"I mark everything down," Dr. Ippolito said. "Bad or good, I mark it down. If a man has gonorrhea, that's marked down, and the players know that. Nothing is left out. This does take hours and hours, keeping these records up to date, but you've got to do it."

Careful records are also kept of medications and any untoward reactions.

Transfer of Records

Each player signs an agreement that if he leaves the Browns, his medical records may be transferred, Dr. Ippolito said.

In the future he would like to do cardiac stress testing on all the players, not just the older ones.

He is continuing sickle cell anemia testing, "although I don't think you ever see true sickle cell anemia in a professional athlete." Many players carry the trait, however, and this is important information for them to have should they marry someone who also has the trait, Dr. Ippolito pointed out.

The SMA-12 testing, which might seem excessive to some physicians, has proved valuable, he reported, and has uncovered the fact, for example, that about 5 per cent of the players have high uric acid levels.

Survival With Totally Artificial Heart Raised to 94 Days in Calf Experiment

Medical Tribune Report

SALT LAKE CITY—Survival time with the totally artificial heart in experimental animals is about 1,500 times greater now than it was 17 years ago.

Survival time in 1958 with totally artificial hearts was 90 minutes; in 1974 it reached 94 days, according to Dr. Jacob Kolff, of the University of Utah College of Medicine.

In May, 1974, Dr. Kolff said, his laboratory implanted the first polyurethane heart of the Jarvik III design. "Overwhelming infection" ended this experiment nine days later, but in the same month a second polyurethane heart was implanted in a calf called "Burk," who lived for 94 days until he was sacrificed.

Flail Chest Treatment



A new treatment for flail chest caused by multiple fractures of the ribs or sternum has been developed by Dr. J. Kent Trinkle, of the University of Texas. It is said to reduce mortality, complications, and hospitalization. Animal studies showed that chest wall instability is usually a minor part of the respiratory defect. The major problem is underlying pulmonary contusion. Above, x-ray of a 23-year-old woman auto accident victim who had bilateral hemopneumothorax with 12 rib fractures and bilateral flail chest. She was treated with nasotracheal suction, fluid restriction, diuretics, methylprednisolone and maintenance of blood volume with whole blood and plasma instead of tracheal intubation and mechanical ventilation.

By Olden

IMMATERIA MEDICA

The Joy of Alex

Dr. Alexander Thomson, of the medical advisory department of Lederle Laboratories has called our attention to the table of contents of the October *Journal of the American Geriatrics Society*, where a line reads:

Sexuality in Old Age. A. Comfort. It's things like that that always prompt us to refer to sexologist A. Comfort as Dr. Alex.

Hot Dogging It

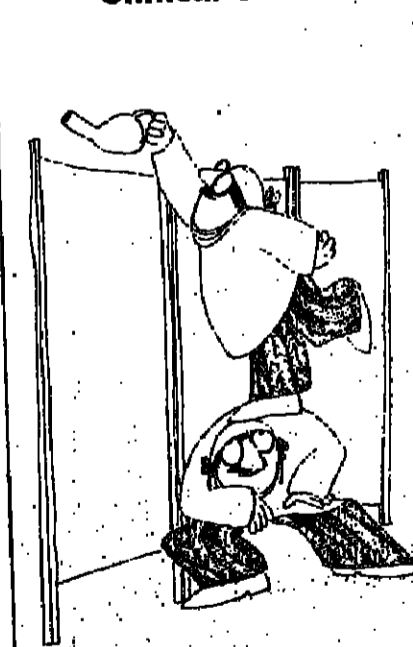
Our skiing friends have been telling us that when a skier comes down the jump slope and does a somersault, a backflip, or whatever in midair, he's "hotdogging" it.

But Peter Albertson, who is one of MEDICAL TRIBUNE's special correspondents, has just sent us, from American College of Cardiologists' meeting in Houston, Tex., a paper with the following sentence in the lead paragraph underlined:

"To determine if the left ventricle itself is altered independent of coronary vascular disease, young beagles were smoked for up to 22 months."

Now that's real hotdogging.

Clinical Cliche



"We ran urines on six patients." © 1975, Medical Tribune, Inc.

Salerno, Normandy, Iwo Jima, Inchon.

And still one more battle...



Top, left to right: Medal of Honor (Army), Silver Star, Legion of Merit. Bottom, left to right: Bronze Star, Air Medal, Purple Heart. Permission to reproduce medals granted by U.S. Department of Defense.

References

1. Effects of treatment on morbidity in hypertension: Results in patients with diastolic blood pressures averaging 115 through 129 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 202: 1028-1034, 1967.
2. Effects of treatment on morbidity in hypertension: II. Results in patients with diastolic blood pressures averaging 90 through 114 mm Hg. Veterans Administration Cooperative Study Group on Antihypertensive Agents. *JAMA* 213: 1143-1152, 1970.
3. Russell RP: Hypertension, in Harvey AM, Johns RJ, Owens AH, et al (eds): *The Principles and Practice of Medicine*, 16th ed. New York, Appleton-Century-Crofts, 1972, pp 331-334.
4. Gilford RW: Drugs for arterial hypertension, in Modell W (ed): *Drugs of Choice*, 1972-1973. St. Louis, The CV Mosby Co, 1972, pp 390-393.
5. Sellers AM, Itskovitz HD, Lindauer MO: Systemic arterial hypertension, in Conn HL Jr, Horwitz O (eds): *Cardiac and Vascular Diseases*, Philadelphia, Lea & Febiger, 1971, vol II, pp 934-943.

Ser-Ap-Es®

reserpine 0.1 mg
hydralazine hydrochloride 25 mg
hydrochlorothiazide 15 mg

INDICATIONS

Hypertension. (See box warning.)

WARNING

This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

CONTRAINDICATIONS

Reserpine: Known hypersensitivity; mental depression (especially with suicidal tendencies); active peptic ulcer; ulcerative colitis; electroconvulsive therapy.

Hydralazine: Hypersensitivity; coronary artery disease; mitral valvular rheumatic heart disease.

Hydrochlorothiazide: Anuria; hypersensitivity to this or other sulfonamide-derived drugs. The routine use of diuretics in an otherwise healthy pregnant woman with or without mild edema is contraindicated and possibly hazardous.

WARNINGS

Reserpine: Use with extreme caution in patients with a history of mental depression. Discontinue at first signs of despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide. MAO inhibitors should be avoided or used with extreme caution.

Hydralazine: Chronic administration of doses over 400 mg daily may produce an arthritis-like syndrome resembling acute systemic lupus erythematosus. This may also occur at lower doses. Long-term treatment with hydralazine may be necessary and residues have been detected many years later. CBC's, L, E, cell preparations and antinuclear antibody titer determinations are indicated before and periodically during prolonged therapy with hydralazine or if the patient develops any unexplained signs or symptoms.

Use MAO inhibitors with caution. Hydrochlorothiazide: Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

Thiazides may be additive or potentiative of the action of other antihypertensive drugs. Potentiation occurs with ganglionic or other autonomic blocking drugs.

Sensitivity reactions are more likely to occur in patients with a history of allergy or bronchial asthma.

The possibility of exacerbation or activation of systemic lupus erythematosus has been reported.

Usage in Pregnancy: Reserpine: The safety of reserpine for use during pregnancy or lactation has not been established. Therefore, the drug should be used in pregnant patients or women of childbearing potential only when, in the judgment of the physician, it is essential to the welfare of the patient.

Increased respiratory tract secretions, nasal congestion, cyanosis, and anorexia may occur in neonates and breast-fed infants of reserpine-treated mothers since reserpine crosses the placental barrier and appears in maternal breast milk.

Hydralazine: The drug should be used only when, in the judgment of the physician, it is deemed essential to the welfare of the patient.

Hydrochlorothiazide: Usage of thiazides in women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult.

Nursing Mothers: Thiazides cross the placental barrier and appear in cord blood and breast milk.

PRECAUTIONS: Reserpine: Use cautiously in patients with history of peptic ulcer, ulcerative colitis, or anastomosis (allergic colic may be precipitated).

Exercise caution when treating hypertensives with renal insufficiency. Use cautiously with digitalis and quinidine. Intraoperative hypotension has occurred in hypertensive patients receiving reserpine does not assure that circulatory instability will not occur in such patients.

Hydralazine: Use cautiously in suspected coronary artery or other cardiovascular disease, cerebral vascular accident, and advanced renal damage. Postural

hypotension may occur, and the pressor response to epinephrine may be reduced. Peripheral neuritis, evidenced by paresthesias, numbness, and tingling, has been observed. Published evidence suggests an antipyretic effect and addition of pyridoxine to the regimen if symptoms develop.

Blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura, have been reported. If such abnormalities develop, discontinue therapy.

Periodic blood counts are advised during prolonged therapy. Hydrochlorothiazide: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. Observe patients for clinical signs of fluid or electrolyte imbalance (hypotension, hypokalemia, hyponatremia, hypocalcemia). Serum and urine electrolyte determinations are particularly important when the patient is vomiting, receiving diuretics, or receiving other drugs that may interfere with adequate oral intake.

also influence serum electrolytes. Warning signs are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pain or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbance such as nausea or vomiting. Hypokalemia may develop with thiazides as with any other potent diuretic, especially during brisk diuresis, when severe cirrhosis is present, or during concomitant administration of steroids or ACTH.

Interference with adequate oral intake of electrolytes will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver diseases or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction rather than administration of salt, except in rare instances when the

hypotremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Transient elevations in plasma calcium may occur in patients receiving thiazides, particularly in those with hyperparathyroidism. Pathological changes in the parathyroid gland have been reported in a few patients on prolonged thiazide therapy. Hyperuricemia may occur or frank gout may be precipitated in certain patients; insulin requirements in diabetic patients may be increased, decreased, or

unchanged. Latent diabetes may become manifest during thiazide administration.

Thiazide drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the post-sympathectomy patient. Thiazides may decrease arterial responsiveness to norepinephrine. This is not sufficient to preclude effectiveness of the pressor agent for therapeutic use.

If nitrogen retention indicates onset of progressive renal impairment, consider withholding or discontinuing diuretic therapy.

Thiazides may decrease serum PBI levels without signs of thyroid disturbance.

ADVERSE REACTIONS: Reserpine: Gastrointestinal—hypersecretion, nausea, vomiting; anorexia, diarrhea. Cardiovascular—angina-like symptoms; arrhythmias (particularly when used concurrently with digitalis or quinidine); bradycardia. Central Nervous System—drowsiness, depression; nervousness; paroxysmal anxiety; nightmares; rare Parkinsonian syndrome and other extrapyramidal tract symptoms; CNS sensitization (manifested by dull sensation, dizziness, gait, ataxia, vertigo, and optic atrophy). Miscellaneous—frequently nasal congestion, pruritus, rash, dryness of mouth, dizziness, headache, dyspnea; syncope; epistaxis; purpura and other hematological reactions; impotence or decreased libido; dysuria; muscular aches; conjunctival injection; weight gain; breast engorgement; pseudotumor; gynecomastia; rarely water retention with edema in hypertensive patients.

Hydralazine: Common—headache; palpitations; anorexia; nausea; vomiting; diarrhea; tachycardia; angina pectoris. Less frequent—nasal congestion; flushing; lacrimation; conjunctivitis; peripheral neuritis, evidenced by paresthesias, numbness, and tingling; edema; dizziness; tremor; muscle cramps; psychologic reactions characterized by depression, disorientation, or anxiety; hypersensitivity (including rash, urticaria, pruritus, fever, chills, arthralgia, eosinophilia, and rarely, hepatitis); constipation; difficulty in micturition; dyspnea; paralytic ileus; lymphadenopathy; splenomegaly; blood dyscrasias, consisting of reduction in hemoglobin and red cell count, leukopenia, agranulocytosis, and purpura; hypotension; paroxysmal pressor response.

Hydrochlorothiazide: Gastrointestinal—nausea, vomiting, anorexia, constipation, jaundice (intrahepatic cholestatic), pancreatitis. Central Nervous System—dizziness, vertigo, paresthesias, headache, xanthopsia. Dermatologic—hypersensitivity—purpura, photosensitivity, rash, urticaria, necrotizing angitis, Stevens-Johnson syndrome, and other hypersensitivity reactions. Hematologic—leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. Cardiovascular—orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, or narcotics. Other—hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness. Whenever adverse reactions are moderate or severe, reduce dosage or withhold therapy.

DOSEAGE: As determined by individual titration (see box warning). Usual dosage is 1 or 2 tablets i.d. For maintenance, adjust dosage to lowest patient requirement. When necessary, more potent antihypertensives may be added gradually in dosages reduced by at least 50 percent.

HOW SUPPLIED: Tablets (dark salmon pink, dry-coated), each containing 0.1 mg reserpine, 25 mg hydralazine hydrochloride, and 15 mg hydrochlorothiazide; bottles of 30, 60, 100 and 1000.

Consult complete literature before prescribing.

CIBA Pharmaceutical Company Division of CIBA-GEIGY Corporation Summit, New Jersey 07991

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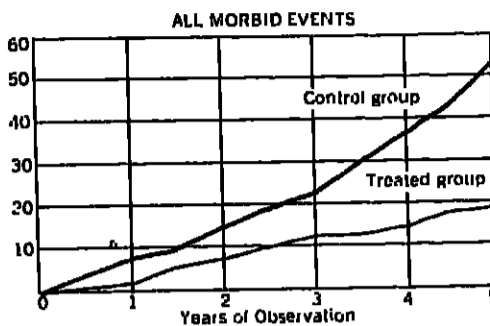
CIBA

The battle against hypertension...

The VA studies demonstrated the need for therapy.^{1,2}

In the VA study of 1967,¹ the patients were 143 male veterans with diastolic pressures averaging 115 through 129 mm Hg. In this group of patients with moderately severe elevations of pressure, antihypertensive therapy appeared to exert significant benefit.¹

Further, in the study of 1970,² which examined effects of treatment in males with diastolic pressures averaging 90 through 114 mm Hg, it was found that even at these lower hypertensive ranges therapy exerted a beneficial effect.² The estimated risk of developing a morbid event over a 5-year period was reduced from 65% to 15%. Degree of benefit was related to prerandomization blood pressure levels.²



Estimated cumulative incidence of all morbid events over a five-year period as calculated by life-table method for patients with diastolic pressures averaging 90-114 mm Hg.

(Adapted)

Control was achieved^{1,2} with...

hydrochlorothiazide

provides a mild antihypertensive effect through control of fluid volume; potentiates the activity of other antihypertensive agents.^{3,4}

(a) Symbolized reduction in circulating fluid volume

plus reserpine

lowers blood pressure through sympathetic inhibition;^{5,6} also produces a central sedative effect which may prove particularly useful in the management of the stress-reactive patient.

(b) Scheme of norepinephrine depletion at sympathetic nerve ending



plus hydralazine

the unique action of hydralazine lowers blood pressure through direct arteriolar vasodilation to reduce peripheral resistance.^{7,8}

(c) Diagram of relaxed arteriole

Only one antihypertensive agent contains all three components used in the two published VA cooperative studies.^{1,2}

In the VA studies, Ser-Ap-Es was not used. However, all the components of Ser-Ap-Es were used in varying combinations and dosages.^{1,2}

Ser-Ap-Es contains all the antihypertensive medication many patients will need.

And when the dosage of each component corresponds to the dosages preestablished by individualized titration, Ser-Ap-Es may prove more convenient and more economical.

The basic drugs used in the VA studies—hydrochlorothiazide, reserpine, and hy-

dralazine—are original products of CIBA research.

Note: Use Ser-Ap-Es cautiously in patients with advanced renal damage or cerebrovascular accident. Discontinue at first sign of mental depression.

Ser-Ap-Es®

reserpine 0.1 mg
hydralazine hydrochloride 25 mg
hydrochlorothiazide 15 mg

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